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Concise syntheses of bridged morpholines.

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ARTICLE

Concise Syntheses of Bridged Morpholines

Andrey V. Zaytsev,[a] James E. Pickles,[b] Suzannah J. Harnor,[b] Alistair P. Henderson,[a] Mohammed Alyasiri,[b] Paul G. Waddell,[c] Celine Cano,[b] Roger J. Griffin,[b,†] and Bernard T. Golding*[a,b]

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Concise and practical syntheses of 8-oxa-3-aza-bicyclo[3.2.1]octane and 9-oxa-3-aza-bicyclo[3.3.1]nonane are described starting from furan-2,5-dicarboxylic acid and 4*H*-pyran-2,6-dicarboxylic acid, respectively, and using a solvent-free step for a key cyclisation.

Introduction

The morpholino unit is a privileged fragment[1] in numerous drugs[2] by virtue of its preferred chair conformation, oxygen lone pairs that can act as hydrogen bond acceptor(s) and a nitrogen atom that enables attachment to an aromatic or heteroaromatic scaffold. The importance of morpholino groups and especially their pseudoequatorial lone pair has recently been highlighted for inhibitors of phosphatidylinositol 3-kinases (PI3Ks) and phosphatidylinositol 3-kinase-related protein kinases (PIKKs).[3] The interaction of the morpholino group of an inhibitor with its target was described as 'representing a cornerstone in drug development of novel PI3K inhibitors'.[3] To modulate the properties of a morpholino unit in such inhibitors, one or more of the methylene groups may be substituted, which has enabled selectivity to be achieved amongst members of the PI kinase families. Thus, selectivity for mTOR (the mammalian target of rapamycin) over PI3Kα, was attained by replacing a morpholino unit in certain pyrazolopyrimidines with the bridged morpholine 8-oxa-3-aza-bicyclo[3.2.1]octane **1a**.[4] This morpholine analogue has also been used to introduce a bridged morpholino group into other compounds targeting mTOR,[5] as well as inhibitors of Aurora kinases[6] and glucokinase.[7] Such modifications permit the properties of inhibitors to be modulated, e.g. cLogP is increased and a subtle structural feature is incorporated. For the mTOR pyrazolopyrimidine inhibitors with a bridged morpholine in place of the parent morpholine, hydrophobic interactions with the kinase's critical 'hinge' region were enhanced.[4]

Results and Discussion

Owing to the current pharmaceutical interest in conformationally constrained ('bridged') morpholines, new synthetic methods to access these compounds have recently been developed.[8-10] Two exemplars are the bridged morpholines 8-oxa-3-aza-bicyclo[3.2.1]octane **1a** and 9-oxa-3-aza-bicyclo[3.3.1]nonane **2a**. The latter compound has only been described as *N*-substituted derivatives in patents.[11] Compared to **1a**, morpholine **2a** provides a significant increase in cLogP (~ 0.4) and the possibility of an enhanced interaction at a hydrophobic binding site of a target protein.

The synthesis of **1a** has been previously achieved by reducing 5-hydroxymethyl-2-furfural to 2,5-bis-hydroxymethyl-tetrahydrofuran, the di-*p*-toluenesulfonate of which was treated with ammonia (under pressure at 170 °C) or benzylamine. These methods either afforded **1a** directly in very low yield[12-16] or in better yield (43-64%) *via* an intermediate *N*-benzyl compound, which was subjected to hydrogenolysis.[17] The latter synthesis was scaleable, but required two high-pressure hydrogenations.

We have developed an efficient and rapid synthesis of 8-oxa-3-aza-bicyclo[3.2.1]octane **1a** (Scheme 1) from furan-2,5-dicarboxylic acid **3** *via* **4** and **5** that avoids high-pressure hydrogenation steps and is solvent-free for the key cyclisation step. The synthesis was inspired by Komppa's classical route[18] to 3-aza-bicyclo[3.3.1]nonane **2b**, whereby *cis*-cyclohexane-1,3-dicarboxylic acid **6b** was neutralised with aqueous ammonia and the solution evaporated presumably to give **7b**, which was heated at ~ 300 °C affording imide **8b**. Compound **8b** was reduced to **2b**, either electrolytically under strongly acidic conditions[18] or with lithium aluminium hydride.[19] This route to **2b** was modified in the manner described below for **1a**, again starting from *cis*-cyclohexane-1,3-dicarboxylic acid and proceeding *via* **6b** and **7b** (see Scheme 2 and Supplementary Information).

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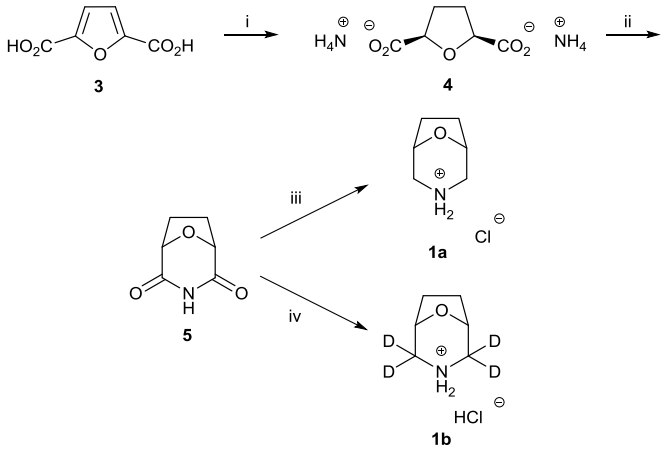
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

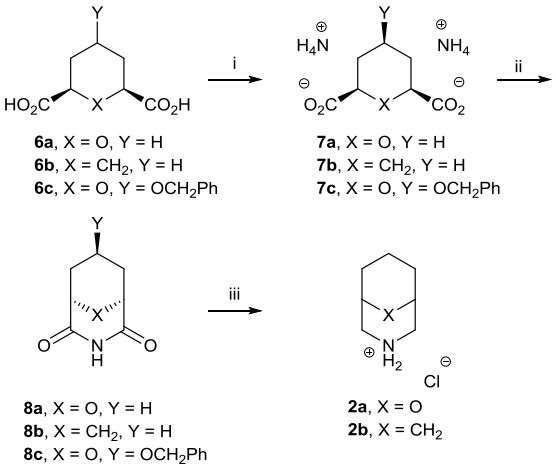


Scheme 1: ***Reagents and Conditions*** i) Pd/C, H_2, AcOH, 60 °C, 69 h, then aq. NH_3, RT, 30 min, 100%; ii) 230 °C (stirred solid), 6 h, 78%; iii) BH_3 in THF, 67 °C, 2 h, then HCl in MeOH, 70 °C, 3 h, 70%; iv) BD_3 in THF, 67 °C, 24 h; then HCl in MeOH, 70 °C, 3 h, 30%.

The route to **1a** parallels that for **2b** and is convenient on a laboratory scale, as well as being applicable to the synthesis of other bridged morpholines exemplified here by an analogous synthesis of **2a**. Catalytic hydrogenation of furan-2,5-dicarboxylic acid **3** was performed at atmospheric pressure in acetic acid at 60 °C to give (2*R*,5*S*)-tetrahydrofuran-2,5-dicarboxylic acid **4**, which was isolated as its crystalline di-ammonium salt in almost quantitative yield. The configuration of **4** was assigned by analogy with that of compound **6a** (see below). Thermolysis of the di-ammonium salt of **4** using either microwave or conventional heating gave 8-oxa-3-aza-bicyclo[3.2.1]octane-2,4-dione **5** (Scheme 1). Optimisation of the reaction conditions enabled imide **5** to be prepared in up to 78% yield, using conventional heating of **4**. A variety of solvents and conditions was explored for the conversion of **4** into **5**, but none provided a higher yield than heating at 230 °C the melt derived from the neat solid of **4**. Finally, reduction of imide **5** with borane gave the desired bridged morpholine **1a**, which was isolated as its hydrochloride in 70% yield. None of the steps in this sequence required chromatographic purification.

In a similar manner (Scheme 2), the readily available 4*H*-pyran-2,6-dicarboxylic acid[20] was reduced (H_2, cat. Pd/C) to (2*R*,6*S*)-tetrahydro-2*H*-pyran-2,6-dicarboxylic acid **6a**, which was isolated as crystals of the di-ammonium salt **7a**. The configuration of the diacid was previously assigned by Cope and Fournier[20] and was confirmed by the crystal structure analysis (CCDC: 1471854; for data see Table 1, Supplementary Information) of the di-ammonium salt **7a**, which showed a chair conformer with both carboxyl groups equatorial (Figure 1). In this structure the protons of the acid groups have been modelled as disordered over two positions along the intermolecular hydrogen bond vectors in such a way that the structure with the highest occupancy is a co-crystal of both the deprotonated and doubly-protonated forms.

Thermolysis of **7a** gave 9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione **8a**, which was reduced with borane to afford 9-oxa-3-aza-bicyclo[3.3.1]nonane **2a**, isolated as its crystalline hydrochloride. A similar cyclisation of diammonium (2*R*,4*s*,6*S*)-4-(benzyloxy)-tetrahydro-2*H*-pyran-2,6-dicarboxylate **7c** gave (1*R*,5*S*,7*s*)-7-(benzyloxy)-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione **8c** (see Supplementary Information for the synthesis of **6c**).



Scheme 2: ***Reagents and Conditions*** i) Aq. NH_3, RT, 2 h, 98%; ii) 230 °C (stirred solid heated), 6 h, 76%; iii) BH_3 in THF, 67 °C, 2.5 h, then HCl in Et_2O, 70 °C, 3 h, 68%.

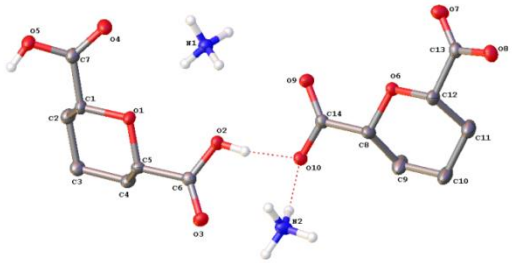


Figure 1: The asymmetric unit of the crystal structure of **7a** (di-ammonium salt). Only the carboxylic acid protons with the highest occupancy are shown for clarity. Thermal ellipsoids are drawn at the 50% probability level.

Conclusions

Syntheses of 8-oxa-3-aza-bicyclo[3.2.1]octane **1a** and 9-oxa-3-aza-bicyclo[3.3.1]nonane **2a** were each rapidly and simply achieved with an overall yield of 50-55% without any hazardous steps, laborious purifications or costly reagents. The key cyclisation step is solvent-free. The developed methodology was also used to prepare [2,2,4,4-$^2H_4$]8-oxa-3-aza-bicyclo[3.2.1]octane **1b** (Scheme 1), which is potentially useful for metabolic studies of drugs containing the bridged morpholine unit derived from **1a**. The method described is versatile being applicable to both cycloalkane-1,3-dicarboxylates[18,19] and oxacycloalkane-1,3-dicarboxylates.

Acknowledgements

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Contributions

BTG, RJG and AVZ conceived this study; AVZ and JEP contributed equally to the experimental work assisted by APH and MA; PGW determined the crystal structure; BTG wrote the paper assisted by AVZ, CC, SJH and JEP.

Notes and references

1 A. A. Alex and R. I. Storer, *Drugs and Their Structural Motifs*, Royal Society of Chemistry, Cambridge, UK, 2010, 1-60.
2 V. A. Pal'chikov, *Russ. J. Org. Chem.*, 2013, **49**, 787.
3 M. Andrs, J. Korabecny, D. Jun, Z. Hodny, J. Bartek and K.Kuca, *J. Med. Chem*., 2015, **58**, 41.
4 A. Zask, J. Kaplan, J. C. Verheijen, D. J. Richard, K. Curran, N. Brooijmans, E. M. Bennett, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustian and K. Yu, *J. Med. Chem*. 2009, **52**, 7942.
5 A. M. Venkatesan, Z. Chen, O. D. Santos, C. Dehnhardt, E. D. Santos, S. Ayral-Kaloustian, R. Mallon, I. Hollander, L. Feldberg, J. Lucas, K. Yu, I. Chaudhary and T. S. Mansour, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5869 and papers cited therein; A. Poulsen, H. Nagaraj, A. Lee, S. Blanchard, C. K. Soh, D. Chen, H. Wang, S. Hart, K. C. Goh, B. Dymock and M. Williams, *J. Chem. Inf. Model*., 2014, **54**, 3238.
6 D. B. Belanger, M. J. Williams, P. J. Curran, A. K. Mandal, Z. Meng, M. P. Rainka, T. Yu, N.-Y. Shih, M. A. Siddiqui, M. Liu, S. Tevar, S. Lee, L. Liang, K. Gray, B. Yaremko, J. Jones, E. B. Smith, D. B. Prelusky and A. D. Basso, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6739.
7 D. J. St. Jean, K. S. Ashton, M. D. Bartberger, J. Chen, S. Chmait, R. Cupples, E. Galbreath, J. Helmering, F.-T. Hong, S. R. Jordan, L. Liu, R. K. Kunz, K. Michelsen, N. Nishimura, L. D. Pennington, S. F. Poon, D. Reid, G. Sivits, M. M. Stec, S. Tadesse, N. Tamayo, G. Van, K. C. Yang, J. Zhang, M. H. Norman, C. Fotsch, D. J. Lloyd and C. Hale, *J. Med. Chem.*, 2014, **57**, 325.
8 R. Bogacki, D. M. Gill, W. J. Kerr, S. Lamont, J. A. Parkinson and L. C. Paterson, *Chem. Commun.*, 2013, **49**, 8931.
9 R. A. Brawn, C. R. W. Guimarães, K. F. McClure and S. Liras, *Org. Lett.*, 2012, **14**, 4802.
10 P. MacLellan and A. Nelson, *Chem. Commun.*, 2013, **49**, 238.
11 *US Patent,* 5 952 324, 1999.
12 F. H. Newth and L. F. Wiggins, *J. Chem. Soc.*, 1948, 155.
13 L. F. Wiggins and D. J. C. Wood, *J. Chem. Soc.*, 1950, 1566.
14 L. F. Wiggins and J. C. Wood, *Nature*, 1949, **164**, 402.
15 A. C. Cope and E. E. Schweizer, *J. Am. Chem. Soc.*, 1959, **81**, 4577.
16 A. C. Cope and W. N. Baxter, *J. Am. Chem. Soc.*, 1955, **77**, 393.
17 T. J. Connolly, J. L. Considine, Z. Ding, B. Forsatz, M. N. Jennings, M. F. MacEwan, K. M. McCoy, D. W. Place, A. Sharma and K. Sutherland, *Org. Proc. Res. Dev.*, 2010, **14**, 459.
18 G. Komppa, *Chem. Ber*., 1932, **65**, 192.
19 L. M. Rice and C. H. Grogan*, J. Org. Chem*., 1958, **23**, 844; Polonski, M. Pham, M. J. Milewska and M. Gdaniec, *J. Org. Chem*., 1996, **61**, 3766.
20 A. C. Cope and A. Fournier, *J. Am. Chem. Soc.*, 1957, **79**, 3896.

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Supporting Information

Experimental Section

General Information

^{1}H, ^{2}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained as solutions in a suitable deuterated solvent and recorded at 500 MHz, 76 MHz and 125 MHz, respectively, on a Bruker Avance III 500 spectrometer. Chemical shifts are reported in parts per million (δ) referenced to the deuterated solvent employed. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), hep (heptet) or combinations thereof. LCMS was carried out on a Waters Acquity SQD operating in positive and negative ion electrospray mode, employing a 50 × 2.1 mm, Waters Acquity UPLC BEH C18, 1.7 μm column and a 1.5 min gradient elution of 0.1% aqueous formic acid and acetonitrile (5–95%) at a flow rate of 0.6 mL min^{-1}. High resolution mass spectrometry were measured using a Finnigan MAT 95 XP or a Finnigan MAT 900 XLT by the EPSRC National Mass Spectrometry Service Centre, University of Wales (Swansea), Singleton Park, Swansea, SA2 8PP. Infrared (IR) spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR as a neat sample. UV spectra were obtained using a U-2001 Hitachi Spectrophotometer with the sample dissolved in ethanol. All commercial reagents and solvents were purchased from reputable suppliers. Where petrol is stated, this refers to the fraction of alkanes, which boils between 40 °C and 60 °C. The chemicals were of the highest available purity and used as supplied unless otherwise stated. Anhydrous solvents were stored under nitrogen. Reactions requiring microwave irradiation were carried out in a Biotage Initiator™ Sixty reactor.

General procedure A

10% Pd/C (~ 10 wt%) was added to the carboxylic acid (for typical scale see below) dissolved in AcOH (1.5 mL/mmol). Following evacuation, an atmosphere of hydrogen was introduced *via* a balloon. After stirring vigorously for 69 h at 60 °C, the suspension was filtered through a Celite plug, eluting with AcOH (1.5 mL/mmol). The solvent was removed

in vacuo and the resultant solid was dissolved in water (0.6 mL/mmol) before the addition of 35% ammonium hydroxide in water (0.6 mL/mmol). The mixture was stirred at RT for 30 min after which it was concentrated and dried *in vacuo* to afford the product.

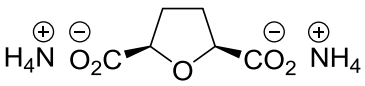
General procedure B

A reaction vessel was equipped with a stirrer bar, finely powdered diammonium salt (for typical scale see below and covered with glass wool. The mixture was stirred and heated at 230 ^{o}C for 6 h. EtOAc (10 mL/mmol) was added along with sat. sodium bicarbonate solution (10 mL/mmol) and the mixture was sonicated to dissolve all the solids. The aqueous layer was extracted twice with EtOAc and the collated organic layers were dried ($MgSO_4$) and evaporated to dryness.

General procedure C

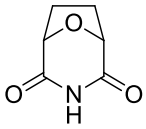
Under an inert atmosphere, to the imide (for typical scale see below) in anhydrous THF (2.3 mL/mmol) was added 1 M BH_3-THF solution (4 mmol per mmol substrate) was added cautiously and the reaction mixture was heated at reflux for 3 h. After cooling to RT, the reaction was quenched MeOH until effervescence ceased, evaporated to dryness and taken up in MeOH (1.7 mL/mmol). A 1.25 M solution of hydrogen chloride in MeOH (1.7 mL/mmol) was added and, under nitrogen, the solution was heated at reflux for 3 h. After cooling to RT, the solvent was removed *in vacuo* and the crude product was purified by recrystallisation from MeOH-diethyl ether.

Diammonium tetrahydrofuran-2,5-dicarboxylate 4:



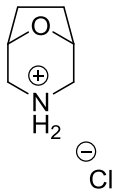
Prepared according to general procedure A with the following reagents: 2,5-furandicarboxylic acid (**3**, 5.00 g, 32.0 mmol), Pd/C (510 mg), AcOH (50 mL), water (20 mL) and 35% ammonium hydroxide in water (20 mL) affording **4** as a white solid (6.06 g, 32.0 mmol, 100%); R_f = 0.51 (DCM:MeOH, 90:10); m.p: 227–230 ^{o}C; IR ν_{max}/cm^{-1} 3178, 2993, 2869, 2778, 1699, 1545; ^{1}H NMR (500 MHz, D_2O) δ 1.73–1.79 (2H, m, 2 × CH), 2.13–2.20 (2H, m, 2 × CH), 4.10–4.16 (2H, m, 2 × CH); ^{13}C NMR (125 MHz, D_2O) δ 30.1, 79.7, 180.4); HRMS calcd. for $C_6H_6O_5$ *m/z* $[M+H]^+$ 159.0296, found 159.0299.

8-Oxa-3-azabicyclo[3.2.1]octane-2,4-dione 5:



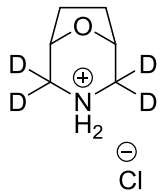
Prepared according to general procedure B starting from **4** (200 mg, 1.03 mmol), which gave **5** as a white solid (110 mg, 0.80 mmol, 78%). R_f = 0.60 (EtOAc); mp: 133–137 ^oC; IR ν_{max}/cm^{-1} 3082, 2839, 1907, 1713; ^1H NMR (500 MHz, DMSO-d_6) δ 1.92–1.97 (2H, m, 2 × CH), 2.13–2.21 (2H, m, 2 × CH), 4.70–4.74 (2H, m, 2 × CH), 11.10 (1H, br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 30.1, 79.7, 180.4; HRMS calcd. for $C_6H_7NO_3$ *m/z* $[M+H]^+$ 142.0499, found 142.0496.

8-Oxa-3-azabicyclo[3.2.1]octane hydrochloride 1a:



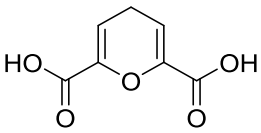
Prepared according to general procedure C with the following reagents: **5** (306 mg, 2.17 mmol), THF (5 mL), 1 M BH_3-THF solution (8.7 mL, 8.7 mmol), MeOH (5 mL), 1.25 M solution of hydrogen chloride in MeOH (6 mL) affording **1a** as an off white solid (0.227 g, 1.52 mmol, 70%); R_f = 0.93 (EtOAc); mp: 192–195 ^oC; IR ν_{max}/cm^{-1} 2958, 2899, 2845, 2768, 2660, 2548, 2492, 2360, 2293, 1598; ^1H NMR (500 MHz, DMSO-d_6) δ 1.91-1.98 (2H, m, 2 × CH), 2.03-2.09 (2H, m, 2 × CH), 2.95-3.06 (4H, m, 4 × CH), 4.37-4.41 (2H, m, 2 × CH), 8.93-9.37 (2H, m, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.6, 47.1, 71.6; HRMS calcd. for $C_6H_{11}NO$ *m/z* $[M+H]^+$ 114.0912, found 114.0913.

8-Oxa-3-azabicyclo[3.2.1]octan-3-ium-2,2,4,4-*d*$_4$ chloride 1b:



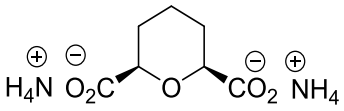
Prepared according to general procedure C with the following reagents: **5** (345 mg, 2.45 mmol), THF (5.6 mL), 1 M BD_3-THF solution (9.79 mL, 9.79 mmol), MeOH (5.6 mL), 1.25 M HCl in MeOH (5.6 mL) yielding **1b** as an off-white solid (113 mg, 0.96 mmol, 30%); R_f = 0.21 (DCM:MeOH, 80:20); mp: 192-198 ^oC; ^1H NMR (500 MHz, DMSO-d_6) δ 1.90-1.97 (2H, m, 2 × CH), 2.04-2.10 (2H, m, 2 × CH), 2.95-3.05 (0.76H,m , non-deuterated material), 4.37-4.41 (2H, m, 2 × CH), 9.38 (2H, br s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.3 (CH_2), 46.3-47.5 (1:2:3:2:1 pent, 2 x CD_2), 72.0 (CH); HRMS calcd. for $C_6H_7D_4NO$ *m/z* $[M+H]^+$ 118.1164, found 118.1161.

4*H*-Pyran-2,6-dicarboxylic acid[1,2]



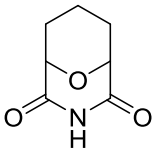
To a stirred solution of tetraethyl 1,5-dioxopentane-1,2,4,5-tetracarboxylate (1.59 g, 4.10 mmol) in water (1.6 mL) was added concentrated hydrochloric acid (1.6 mL). The mixture was heated at reflux for 6 h, after which the solvent was removed in *vacuo*. To the stirred residue was added conc. sulfuric acid (2 mL) dropwise. The mixture was cooled to 0 ^oC and stirred for 18 h. Ice-cold water was added to give a precipitate which was filtered, washed with ice cold water (3 × 10 mL) and dried to give a brown solid. According to ^1H NMR analysis this product was a mixture of the title compound and ethyl ester(s). The mixture was taken up in THF (25 mL) and 2M aqueous NaOH (22.5 mL) was added. After stirring at room temperature overnight, the resulting solution was acidified with 2M HCl. The precipitate was filtered, washed with ice-cold water and dried to afford the title compound as a brown solid (0.50 g, 2.9 mmol, 71%). R_f = 0.15 (DCM:MeOH, 95:5); mp = 250 ^oC dec; λ_{max} (EtOH/nm) 234; IR (neat) ν_{max}/cm^{-1} 3420, 3014, 2845, 1724, 1632; ^1H NMR (500 MHz, DMSO-d_6) δ 3.02 (2H, t, *J* = 3.7 Hz, CH_2), 6.01 (2H, t, *J* = 3.7 Hz), 13.1 (2H, br s, 2 × OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 21.6 (CH_2), 110.2 (CH), 142.2 (CH), 162.2 (C=O); HRMS calcd. for $C_7H_6O_5$ *m/z* $[M+H]^+$ 171.0288, found 171.0288.

Ammonium (2*R*,6*S*)-tetrahydro-2*H*-pyran-2,6-dicarboxylate 6a:



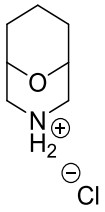
Prepared according to general procedure A with the following reagents: 4*H*-pyran-2,6-dicarboxylic acid (3.47 g, 20.5 mmol), AcOH (70 mL), Pd/C (326 mg), water (35 mL) and 35% ammonium hydroxide solution (6.3 mL). Compound **6a** was an off-white solid (4.16 g, 20 mmol, 98%). R_f = 0.41 (DCM:MeOH, 60:40); mp: 212-220 ^oC; IR ν_{max}/cm^{-1} 2921, 2851, 1561, 1403; ^1H NMR (500 MHz, DMSO-d_6) δ 1.24-1.37 (2H, m, 2 × CH), 1.49-1.62 (1H, m, CH), 1.76-1.93 (3H, m, 3 × CH), 3.66 (2H, dd, J = 2.2 and 10.9 Hz, 2 × CH), 7.90 (8H, br s, 2 × NH_4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 23.9, 29.3, 77.9, 175.1; HRMS calcd. for $C_7H_{10}O_5$ *m/z* $[M+H]^+$ 173.0455, found 173.0459.

9-Oxa-3-azabicyclo[3.3.1]nonane-2,4-dione 7a:



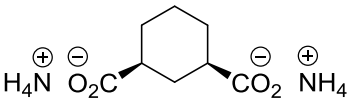
Prepared according to general procedure B starting from **6a** (150 mg, 0.72 mmol) furnishing **7a** as a white solid (85 mg, 0.55 mmol, 76%). R_f = 0.29 (petrol:EtOAc, 60:40); mp: 149-157 ^oC; IR ν_{max}/cm^{-1} 3077, 2958, 2925, 2852, 1702; ^1H NMR (500 MHz, DMSO-d_6) δ 1.35-1.50 (1H, m, CH), 1.66-1.77 (3H, m, 3 × CH), 1.84-1.94 (2H, m, 2 × CH), 4.45 (2H, dd, J = 1.0 and 5.4 Hz, 2 × CH), 11.58 (1H, br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.6, 26.0, 71.3, 173.7; HRMS calcd. for $C_7H_9NO_3$ *m/z* $[M+H]^+$ 156.0655, found 156.0653.

9-Oxa-3-azabicyclo[3.3.1]nonane hydrochloride 2a:



Prepared according to general procedure C with the following reagents: **7a** (585 mg, 3.77 mmol), THF (5 mL), 1 M BH_3-THF (15.1 mL, 15.1 mmol), MeOH (15 mL) and 1 M HCl in Et_2O (30 mL), furnishing **2a** as a white solid (420 mg, 2.56 mmol, 68%). R_f = 0.16 (DCM:MeOH, 80:20); mp: 242-250 ^oC; IR ν_{max}/cm^{-1} 3092, 2753, 2637, 2494, 1591; ^1H NMR (500 MHz, DMSO-d_6) δ 1.56-1.69 (3H, m, 3 × CH), 1.89 (2H, heptet, 2 × CH), 2.00-2.16 (1H, m, CH), 3.19-3.22 (4H, m, 2 × CH_2), 4.03 (2H, br s, 2 × CH), 8.28 (1H, br s, NH), 9.72 (1H, br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 16.7, 27.7, 44.4, 63.8; HRMS calcd. for $C_7H_{13}NO$ *m/z* $[M+H]^+$ 128.1070, found 128.1067.

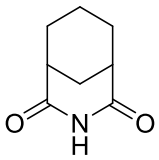
Ammonium (1*R*,3*S*)-cyclohexane-1,3-dicarboxylate 6b:



Prepared according to general procedure A with the following reagents: (1*R*,3*S*)-cyclohexane-1,3-dicarboxylic acid (2.5 g, 14.5 mmol) in water (10 mL) with 35% ammonium hydroxide in water (10 mL). Compound **6b** was a white solid (3.0 g, 14.5 mmol, 100%). R_f = 0.31 (DCM:MeOH, 90:10); mp: 127-134 ^oC; IR ν_{max}/cm^{-1} 2922, 1686; ^1H NMR (500 MHz, DMSO-d_6) δ 1.14-1.35 (4H, m, 4 × CH), 1.74-1.90 (3H, m, 3 × CH), 2.00-2.15 (3H, m, 3 ×

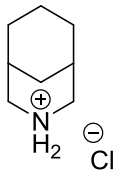
CH), 5.97 (8H, br s, 2 × NH_4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 25.5 (CH_2), 29.7 (CH_2), 33.1, 44.2, 178.1; HRMS calcd. for $C_8H_{10}O_4$ *m/z* $[M+H]^+$ 171.0663, found 171.0667.

3-Azabicyclo[3.3.1]nonane-2,4-dione 7b:



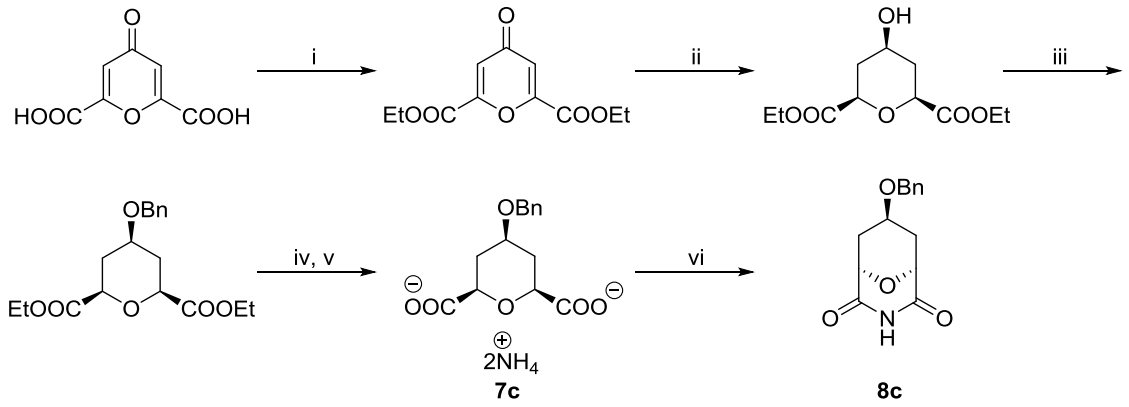
Prepared according to general procedure B from compound **6b** (950 mg, 4.61 mmol). **7b** was a white solid (489 mg, 3.20 mmol, 69%). R_f = 0.63 (DCM:MeOH, 90:10); mp: 123-130 °C; IR ν_{max}/cm^{-1} 2952, 2925, 1696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40-1.51 (2H, m, 2 × CH), 1.60-1.75 (3H, m, 3 × CH), 1.92-1.99 (2H, m, 2 × CH), 2.13-2.20 (1H, m, CH), 7.73-7.78 (2H, m, 2 × CH), 7.84 (1H, br s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 27.9, 28.9, 37.7, 175.8; HRMS calcd. for $C_8H_{11}NO_2$ *m/z* $[M+H]^+$ 154.0863, found 154.0859.

3-Azabicyclo[3.3.1]nonane hydrochloride 2b



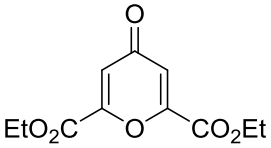
Prepared according to general procedure C with the following reagents: Compound **7b** (289 mg, 1.80 mmol), THF (3 mL), 1 M BH_3-THF (7.5 mL, 7.5 mmol), MeOH (10 mL) and 1 M HCl in MeOH (10 mL) furnishing **2b** as a white solid (200 mg, 1.23 mmol, 69%). R_f = 0.13 (MeOH); mp: 209-214 °C; IR ν_{max}/cm^{-1} 2924, 2674, 1587, 1445; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50-1.79 (8H, m, 8 × CH), 1.86-2.00 (2H, m, 2 × CH), 3.03-3.12 (2H, m, 2 × CH), 3.17-3.23 (2H, m, 2 × CH), 7.67 (1H, br s, NH), 9.29 (1H, br s, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 25.7, 29.2, 30.2, 47.3; HRMS calcd. for $C_8H_{16}N$ *m/z* $[M+H]^+$ 126.1277, found 126.1277.

Synthesis of (1*R*,5*S*,7*s*)-7-(benzyloxy)-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione 8c:



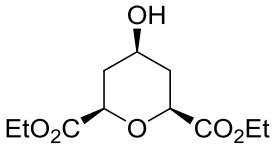
Reagents and Conditions: i) H_2SO_4, EtOH, RT, 48 h, 70%; ii) H_2, Pd/$BaSO_4$, EtOH, RT, 20 h, 67%; iii) $BnOC(NH)CCl_3$, TfOH, DCM:cyclohexane, RT, 24 h, 91%; iv) LiOH, THF, RT, 20 h, 100%; v) NH_4OH, H_2O, RT, 100%; vi) 230 ^oC, 6 h, 37%.

Diethyl 4-oxo-4*H*-pyran-2,6-dicarboxylate



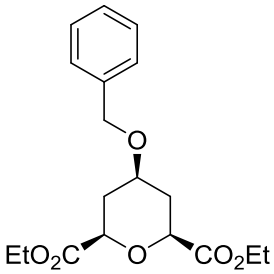
To a solution of 4-oxo-4*H*-pyran-2,6-dicarboxylic acid (1.54 g, 7.61 mmol) in ethanol (30 mL) at 0 ^oC was added conc. sulfuric acid (1.2 mL) dropwise over 5 min. The mixture was warmed to room temperature and then heated at reflux for 48 h. After cooling to RT, the solvent was removed *in vacuo* and the residue taken up into ethyl acetate (5 mL). Saturated sodium hydrogen carbonate was added until the aqueous layer pH was ~ 7. The aqueous layer was extracted with EtOAc (3 × 20 mL); the organic extracts were combined, dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to afford the title compound as an orange oil which was used directly (1.25 g, 5.2 mmol, 70%); R_f = 0.44 (Petrol:EtOAc, 1:1); λ_{max} (EtOH/nm) 271; IR ν_{max}/cm^{-1} 3071, 2984, 1650; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (6H, t, *J* = 7.1 Hz, 2 × CH_3), 4.44 (4H, q, *J* = 7.1 Hz, 2 × CH_2), 7.10 (2H, s, 2 × CH); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.0, 63.2, 120.1, 153.0, 159.4, 177.1; HRMS calcd. for $C_{11}H_{12}O_6$ *m/z* $[M+H]^+$ 241.0707, found 241.0705.

Diethyl (2*R*,4*s*,6*S*)-4-hydroxytetrahydro-2*H*-pyran-2,6-dicarboxylate



To diethyl 4-oxo-4*H*-pyran-2,6-dicarboxylate (1.4 g, 5.82 mmol) in ethanol (20 mL) was added a catalytic quantity of $Pd/BaSO_4$ and the mixture was placed under an atmosphere of hydrogen. After stirring for 20 h, the slurry was filtered through a pad of Celite, which was washed with ethanol (20 mL); the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica, elution with petrol:EtOAc, 1:1) to give the title compound as a colourless oil (0.98 g, 3.79 mmol, 67%); R_f = 0.17 (PE:EA 1:1); IR ν_{max}/cm^{-1} 3497, 3339, 2983, 1719; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (6H, t, *J* = 7.1 Hz, 2 × CH_3), 1.54 (2H, q, *J* = 12.0 Hz, 2 × CH_2), 2.22 -2.32 (2H, m, 2 × CH_2), 2.39 (1H, br s, OH), 3.95 (1H, tt, *J* = 4.5 and 10.9 Hz, CH), 4.01 (2H, dd, *J* = 2.0 and 12.0 Hz, 2 × CH_2), 4.22 (4H, q, *J* = 7.1 Hz, 2 × CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 37.2, 61.5, 67.2, 74.8, 169.7; HRMS calcd. for $C_{11}H_{18}O_6$ *m/z* $[M+H]^+$ 247.1176, found 247.1179.

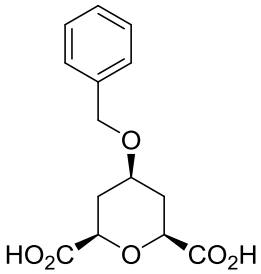
Diethyl (2*R*,4*s*,6*S*)-4-(benzyloxy)tetrahydro-2*H*-pyran-2,6-dicarboxylate[3]



Diethyl (2*R*,4*s*,6*S*)-4-hydroxytetrahydro-2*H*-pyran-2,6-dicarboxylate (1.3 g, 5.3 mmol) was dissolved in DCM (11 mL) and cyclohexane (11 mL). Benzyl trichloroacetamidate (1.09 mL, 5.83 mmol) was introduced dropwise followed by TFA (56 µL) in DCM (0.5 mL). After 15 h, more benzyl trichloroacetamidate (0.55 mL, 2.92 mmol) was added with TFA (38 µL) in DCM (0.5 mL). After a further 4 h at RT, the solvent was removed *in vacuo* and the crude product was purified by MPLC (elution with petrol:EtOAc, 70:30) affording the title compound as a colourless oil (1.6 g, 4.8 mmol, 91%); R_f = 0.53 (petrol:EtOAc, 1:1); IR (neat) ν_{max}/cm^{-1} 1734; ^1H NMR (500 MHz, $CDCl_3$) δ 1.23 (6H, t, *J* = 7.2 Hz, 2 × CH_3), 1.55 (2H, q, *J* = 12.2 Hz, 2 × CH), 2.32-2.39 (2H, m, 2 × CH), 3.61 (1H, tt, *J* = 4.4 Hz and 10.9

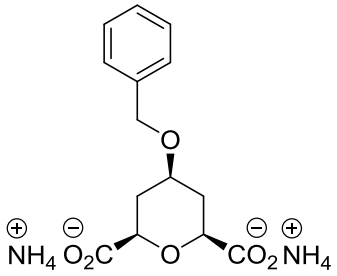
Hz, CH), 4.18 (4H, q, *J* = 7.2 Hz, 2 × CH_2), 4.54 (2H, s, CH_2), 7.20-7.32 (5H, m, 5 × H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 34.6, 61.6, 69.9, 73.4, 75.0, 127.6, 127.9, 128.6, 138.0, 169.7; HRMS calcd. for $C_{18}H_{24}O_6$ *m/z* $[M+H]^+$ 354.1911, found 354.1915.

(2*R*,4*s*,6*S*)-4-(Benzyloxy)tetrahydro-2*H*-pyran-2,6-dicarboxylic acid 6c:



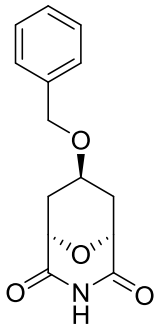
To diethyl (2*R*,4*s*,6*S*)-4-(benzyloxy)tetrahydro-2*H*-pyran-2,6-dicarboxylate (218 mg, 0.60 mmol) in THF (6.5 mL) was added 2 M LiOH in water (4.5 mL, 8.9 mmol) and the mixture was stirred at room temperature for 28 h. The solvent was removed *in vacuo* and the residue taken up in EtOAc (5 mL), H_2O (2 mL) was added and the pH of the aqueous layer was adjusted to 2 with 2M HCl. The product was extracted with EtOAc (3 × 15 mL), the organic extracts were combined and dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford the title compound as a white solid (180 mg, 0.64 mmol, 100%.); R_f = 0.27 (DCM:MeOH, 50:50); mp 165-172 ^oC; IR (neat) ν_{max}/cm^{-1} 3247, 1765, 1711; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.30 (2H, q, *J* = 12.2 Hz, 2 × CH), 2.25-2.30 (2H, m, 2 × CH), 3.74 (1H, tt, *J* = 4.4 Hz and 10.9 Hz, CH), 4.02 (2H, dd, *J* = 1.9 and 12.3 Hz, 2 × CH), 4.57 (2H, s, CH_2), 7.25-7.40 (5H, m, 5 × H-Ar), 12.75 (2H, br s, OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 39.9, 69.3, 73.4, 74.0, 127.8, 127.9, 128.7, 139.2, 171.7; HRMS calcd. for $C_{14}H_{16}O_6$ *m/z* $[M-H]^-$ 279.0874, found 279.0876.

Diammonium (2*R*,4*s*,6*S*)-4-(benzyloxy)tetrahydro-2*H*-pyran-2,6-dicarboxylate 7c:



(2*R*,4*s*,6*S*)-4-(Benzyloxy)tetrahydro-2*H*-pyran-2,6-dicarboxylic acid (700 mg, 2.5 mmol) was solubilised in water (3.5 mL) and 35% ammonium hydroxide in water (3.5 mL) was added dropwise. After stirring for 3 h at RT, the solvent was removed *in vacuo* and by freeze drying, to afford the title compound as a white solid (750 mg, 2.5 mmol, 100%.); R_f = 0.37 (DCM:MeOH, 50:50); mp 234-238 ^oC; IR (neat) ν_{max}/cm^{-1} 3199, 1574; ^1H NMR (500 MHz, DMSO-d_6) δ 1.14 (2H, q, *J* = 11.8 Hz, 2 × CH), 2.31-2.37 (2H, m, 2 × CH), 3.51-3.63 (3H, m, CH and 2 × CH), 4.59 (2H, s, CH_2), 7.20-7.44 (5H, m, 5 × H-Ar), 7.82 (8H, br s, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 36.5, 69.0, 75.6, 76.4, 127.7, 127.8, 128.7, 139.6, 175.1; HRMS calcd. for $C_{14}H_{22}N_2O_6$ *m/z* 279.0874 $[M-H]^-$, found 279.0876.

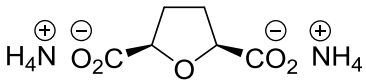
(1*R*,5*S*,7*s*)-7-(benzyloxy)-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione 8c:



(1*R*,5*S*,7*s*)-7-(benzyloxy)-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione was synthesised according to general procedure B, using: diammonium (2*R*,4*s*,6*S*)-4-(benzyloxy)tetrahydro-2*H*-pyran-2,6-dicarboxylate (300 mg, 0.90 mmol) and purification by MPLC (petrol:EtOAc, 70:30) to afford the title compound as a white solid (83 mg, 0.32 mmol, 35%); R_f = 0.57 (EtOAc); mp 164-169 ^oC; IR (neat) ν_{max}/cm^{-1} 3178, 1698; ^1H NMR (500 MHz, $CDCl_3$) 2.07 (2H, dq, *J* = 3.3 and 14.5 Hz, 2 x CH), 2.21-2.34 (2H, m, 2 × CH), 3.78 (1H, pen, *J* = 2.7 Hz, CH), 4.33 (2H, s, CH_2), 4.41 (2H, d, *J* = 6.1 Hz, 2 × CH), 7.12-7.30 (5H, m, 5 × H-Ar), 7.87 (1H, bs, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.9, 68.6, 69.4, 70.0, 126.3, 126.7, 127.4, 136.3, 171.6; HRMS calcd. for $C_{14}H_{15}NO_4$ *m/z* 279.1339 $[M+H]^+$, found 279.1344.

Table 1: Crystal data and structure refinement for **6a**.

Empirical formula	$C_7H_{13}NO_5$
Formula weight	191.18
Temperature/K	150.0(2)
Crystal system	triclinic
Space group	P-1
a/Å	6.9141(2)
b/Å	9.3897(3)
c/Å	14.4781(5)
α/°	101.468(3)
β/°	96.993(3)
γ/°	98.349(3)
Volume/Å^3	900.34(5)
Z	4
ρ_{calc}g/cm^3	1.410
μ/mm^{-1}	1.036
F(000)	408.0
Crystal size/mm^3	0.15 × 0.11 × 0.08
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.306 to 133.746
Index ranges	$-8 \leq h \leq 8$, $-11 \leq k \leq 11$, $-16 \leq l \leq 14$
Reflections collected	12629
Independent reflections	3184 [R_{int} = 0.0253, R_{sigma} = 0.0180]
Data/restraints/parameters	3184/2/275
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0312, wR_2 = 0.0817
Final R indexes [all data]	R_1 = 0.0345, wR_2 = 0.0843
Largest diff. peak/hole / e Å^{-3}	0.26/-0.24



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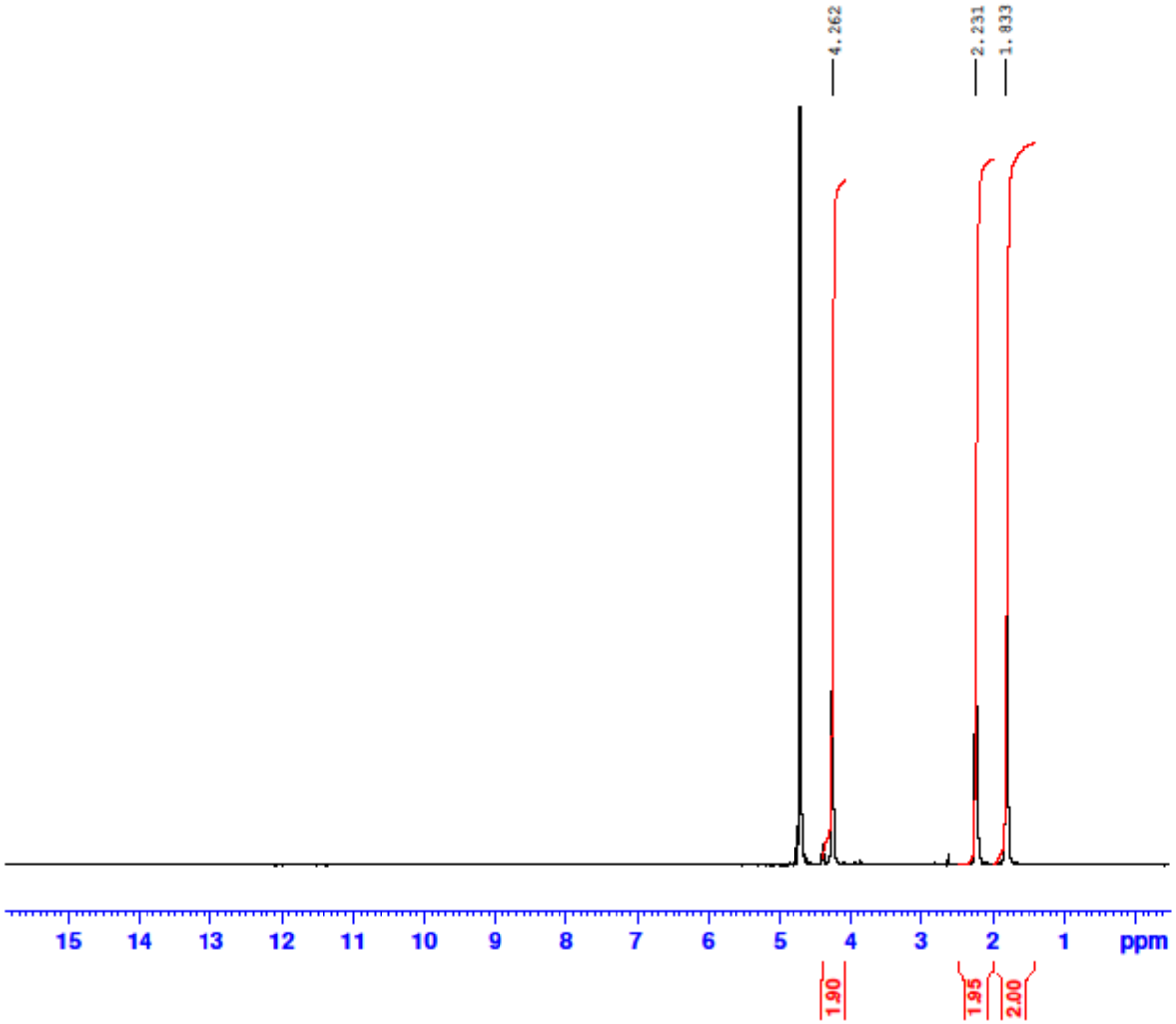

BRUKER

Newcastle University

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EXPNO                 10
PROCNO                 1

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FIDRES        0.157632 Hz
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RG                  144
DW               48.400 usec
DE               11.99 usec
TE               298.1 K
D1            1.00000000 sec
TD0                   1

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NUC1                   1H
P1                 16.25 usec
PLW1         18.33600044 W

F2 - Processing parameters
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LB                 0.30 Hz
GB        0
PC                 1.00
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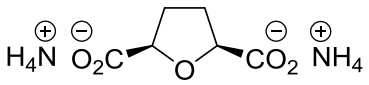
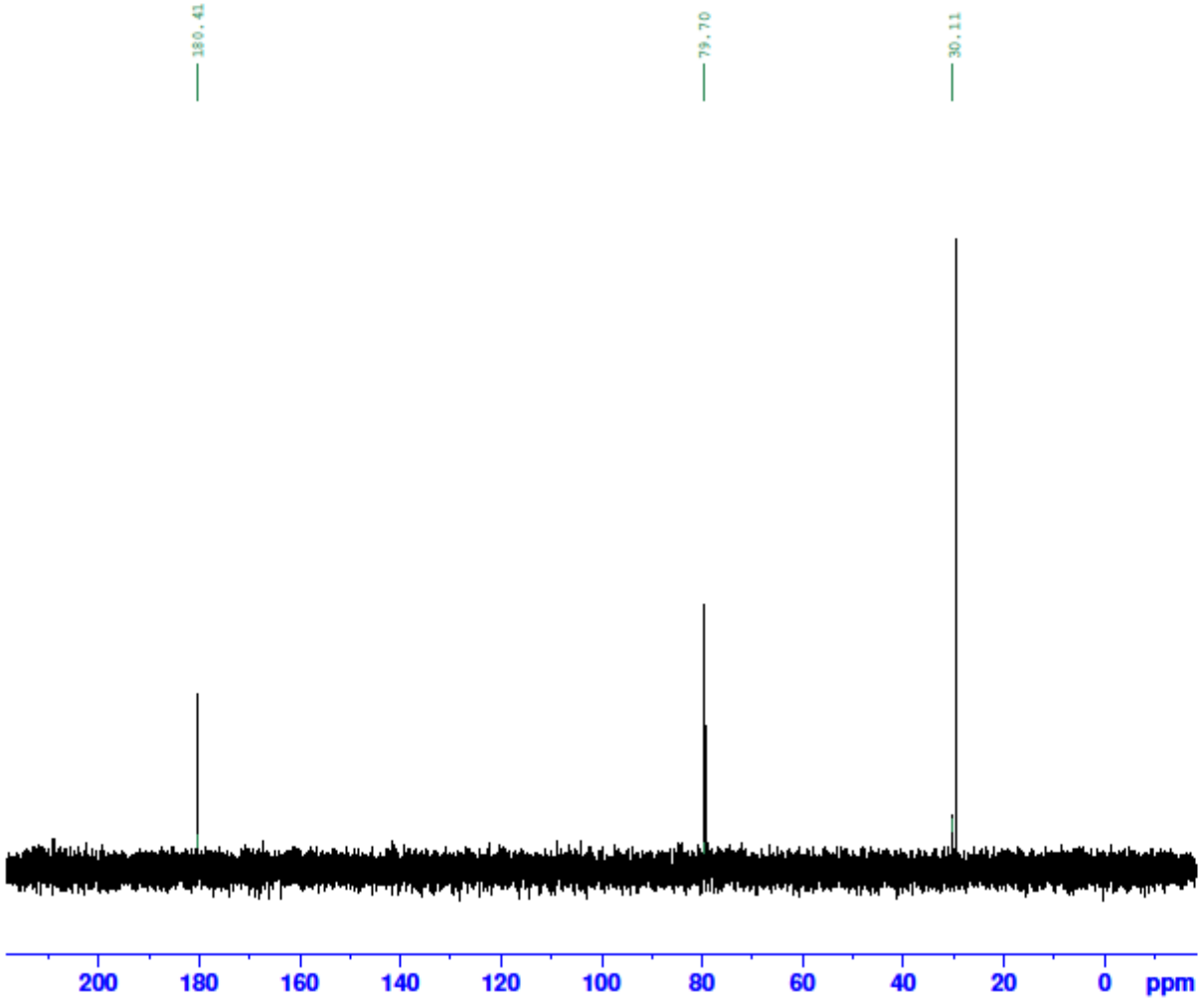


4



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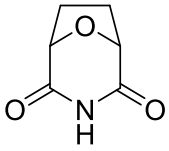
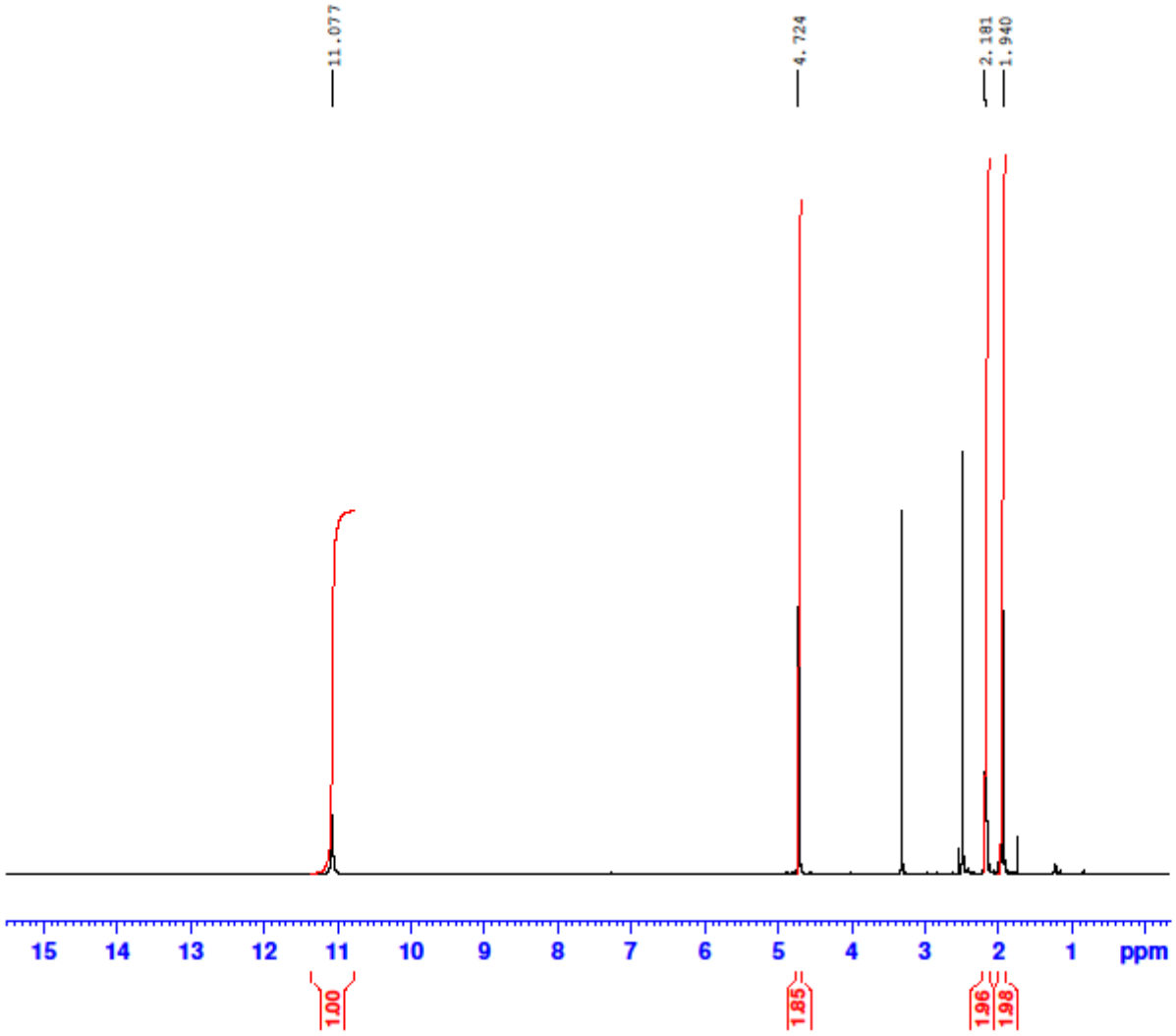
```
Current Data Parameters
NAME       JEP-446-148_2
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150220
Time               9.44
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT             D2O
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                  456
DW               16.800 usec
DE                7.68 usec
TE               298.1 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                65536
SF           125.8005350 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



5



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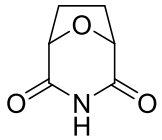
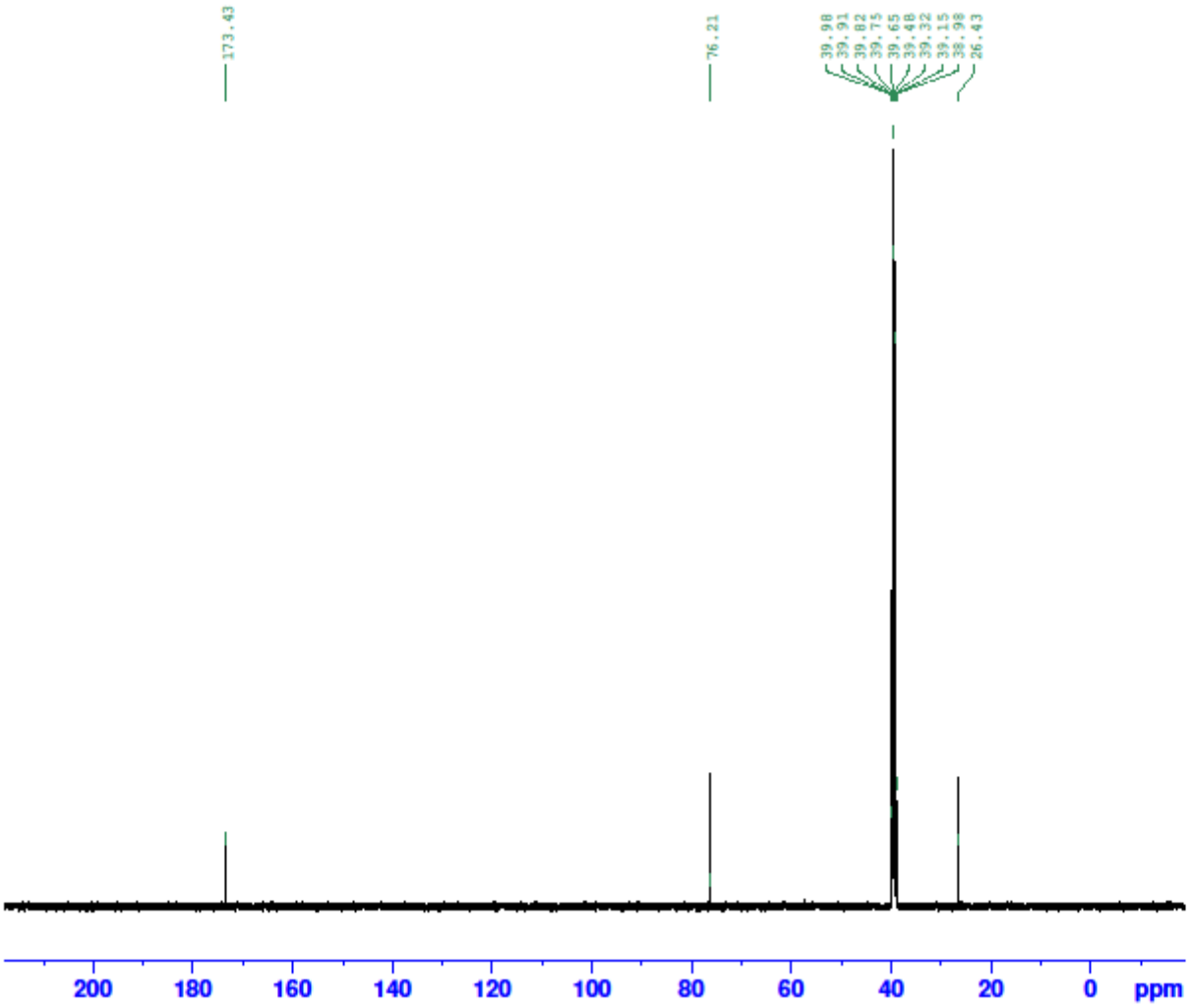
```
Current Data Parameters
NAME      JEP-446-036PURE
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_           20121114
Time              16.37
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT           DMSO
NS                  16
DS                   0
SWH          10330.578 Hz
FIDRES        0.157632 Hz
AQ           3.1719425 sec
RG                 406
DW              48.400 usec
DE              12.35 usec
TE              295.0 K
D1           1.00000000 sec
TD0                 1

======== CHANNEL f1 ========
NUC1                1H
P1              14.50 usec
PL1              1.00 dB
PL1W       18.33646011 W
SFO1       500.3030896 MHz

F2 - Processing parameters
SI               65536
SF          500.3000116 MHz
WDW                 EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```



5



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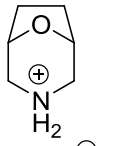
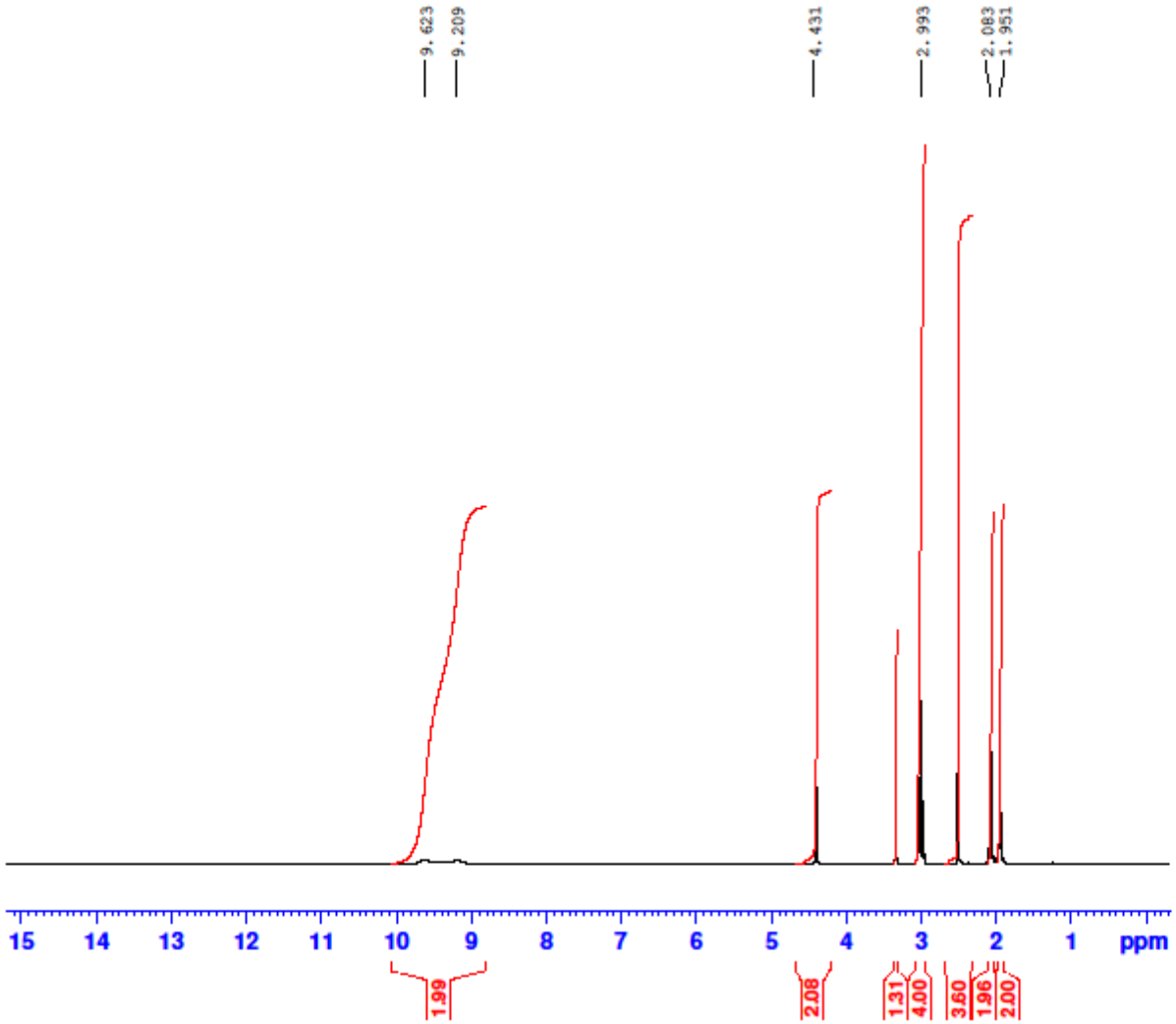
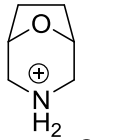
```
Current Data Parameters
NAME        JKP-446-036PURE
EXPNO                    11
PROCNO                    1

F2 - Acquisition Parameters
Date_              20121114
Time                  17.14
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg30
TD                   65536
SOLVENT               DMSO
NS                      256
DS                        2
SWH               29761.904 Hz
FIDRES            0.454131 Hz
AQ                1.1010048 sec
RG                      456
DW                   16.800 usec
DE                    7.68 usec
TE                   295.9 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                    9.75 usec
PL1        0 dB
PL1W          82.38987732 W
SFO1         125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG[2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                   1.00 dB
PL12                 17.00 dB
PL13                 21.00 dB
PL2W          18.33646011 W
PL12W          0.46059108 W
PL13W          0.18336460 W
SFO2         500.3020012 MHz

F2 - Processing parameters
SI                   65536
SF           125.8005979 MHz
WDW                     EM
SSB        0
LB                    1.00 Hz
GB         0
PC                    1.40
```



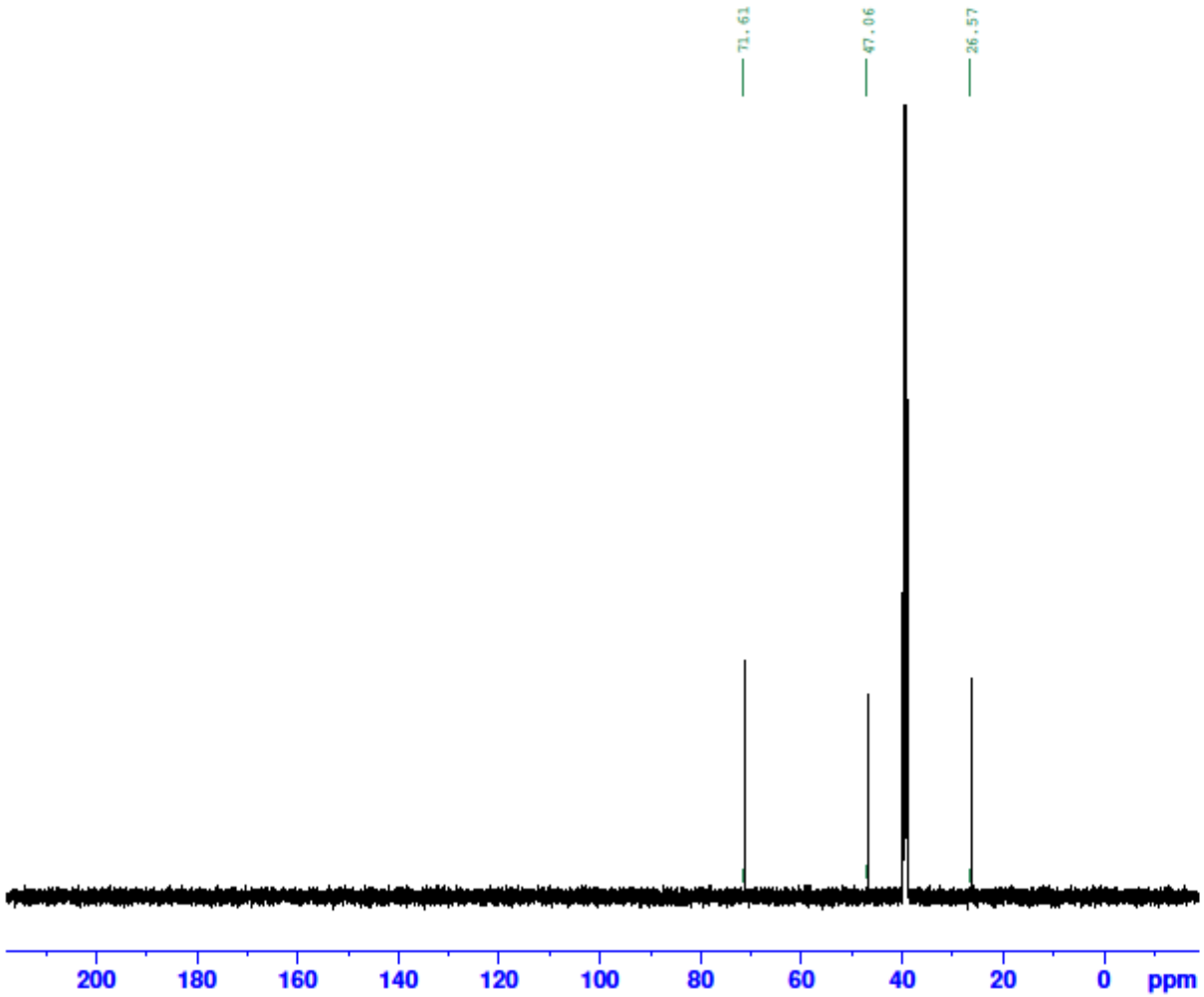
1a



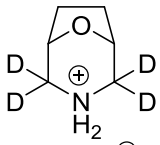

```
Current Data Parameters
NAME      Andreys HAT-morpholine
EXPNO                 10
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121220
Time              13.45
INSTRUM           spect
PROBHD    5 mm PABBO BB-
PULPROG           zg30
TD                65536
SOLVENT           DMSO
NS                   16
DS                    0
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719425 sec
RG                  362
DW               48.400 usec
DE               12.35 usec
TE                297.0 K
D1            1.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                  1H
P1                14.50 usec
PL1                1.00 dB
PL1W        18.33646011 W
SFO1        500.3030896 MHz

F2 - Processing parameters
SI                 65536
SF          500.3000000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```



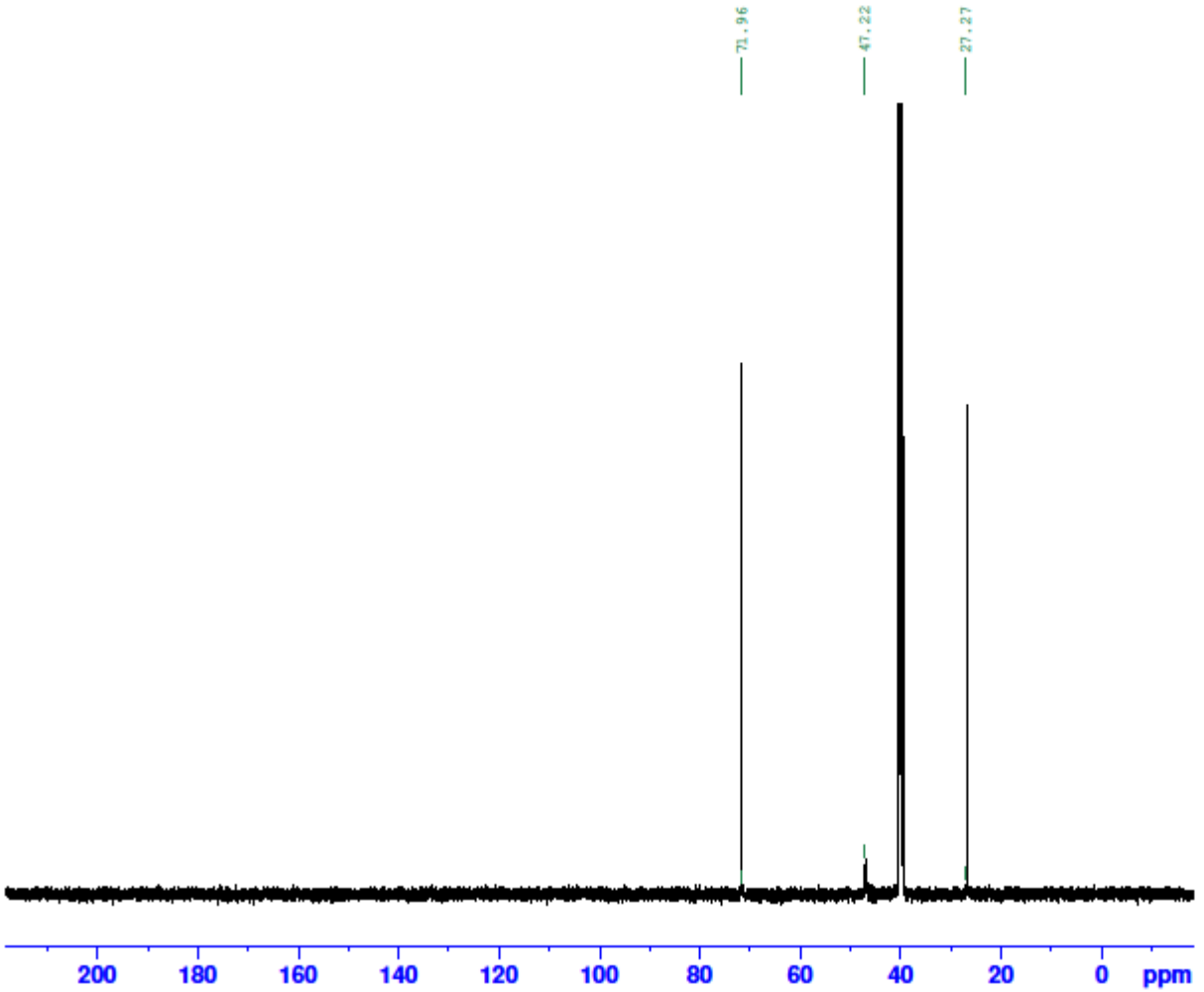
1a




```
Current Data Parameters
NAME      Andreyx HAT-morpholine
EXPNO                 20
PROCNO                 1

F2 - Acquisition Parameters
Date_              20121220
Time                 14.12
INSTRUM              spect
PROBHD     5 mm PABBO BB-
PULPROG            zgpg30
TD                 65536
SOLVENT              DMSO
NS                   256
DS                     2
SWH              29761.904 Hz
FIDRES           0.454131 Hz
AQ               1.1010048 sec
RG                   575
DW                16.800 usec
DE                 7.68 usec
TE                 297.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.75 usec
PL1        0 dB
PL1W        82.38987732 W
SFO1       125.8131151 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 1.00 dB
PL12               17.00 dB
PL13               21.00 dB
PL2W        18.33646011 W
PL12W        0.46059108 W
PL13W        0.18336460 W
SFO2       500.3020012 MHz

F2 - Processing parameters
SI                 65536
SF         125.8005979 MHz
WDW                   EM
SSB        0
LB                  1.00 Hz
GB         0
PC                  1.40
```



1b



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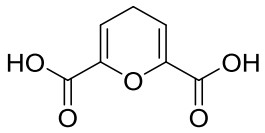
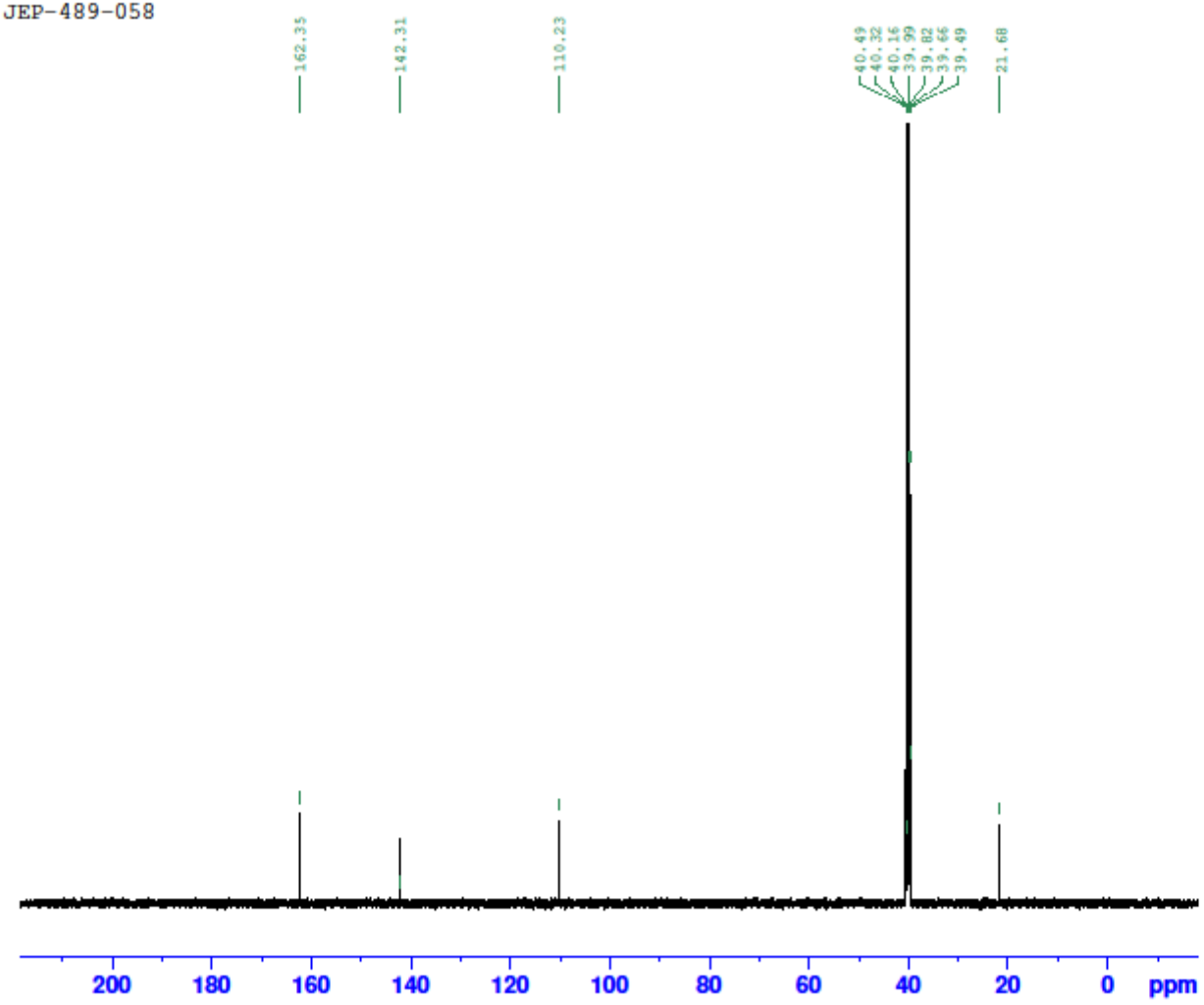
```
Current Data Parameters
NAME          JKP-489-046
EXPNO                 120
PROCNO                  1

F2 - Acquisition Parameters
Date_          20141006
Time               22.25
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg
TD                 41682
SOLVENT             DMSO
NS                  2656
DS                     2
SWH           29761.904 Hz
FIDRES        0.714366 Hz
AQ            0.6999216 sec
RG                   575
DW               16.800 usec
DE                7.72 usec
TE                298.0 K
D1            5.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1                 13C
P1                 9.75 usec
PLW1        82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2        18.33600044 W
PLW12        0.75654000 W
PLW13        0.48418999 W

F2 - Processing parameters
SI                 65536
SF           125.8005350 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.40
```



JEP-489-058



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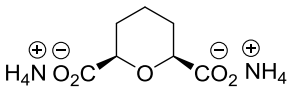
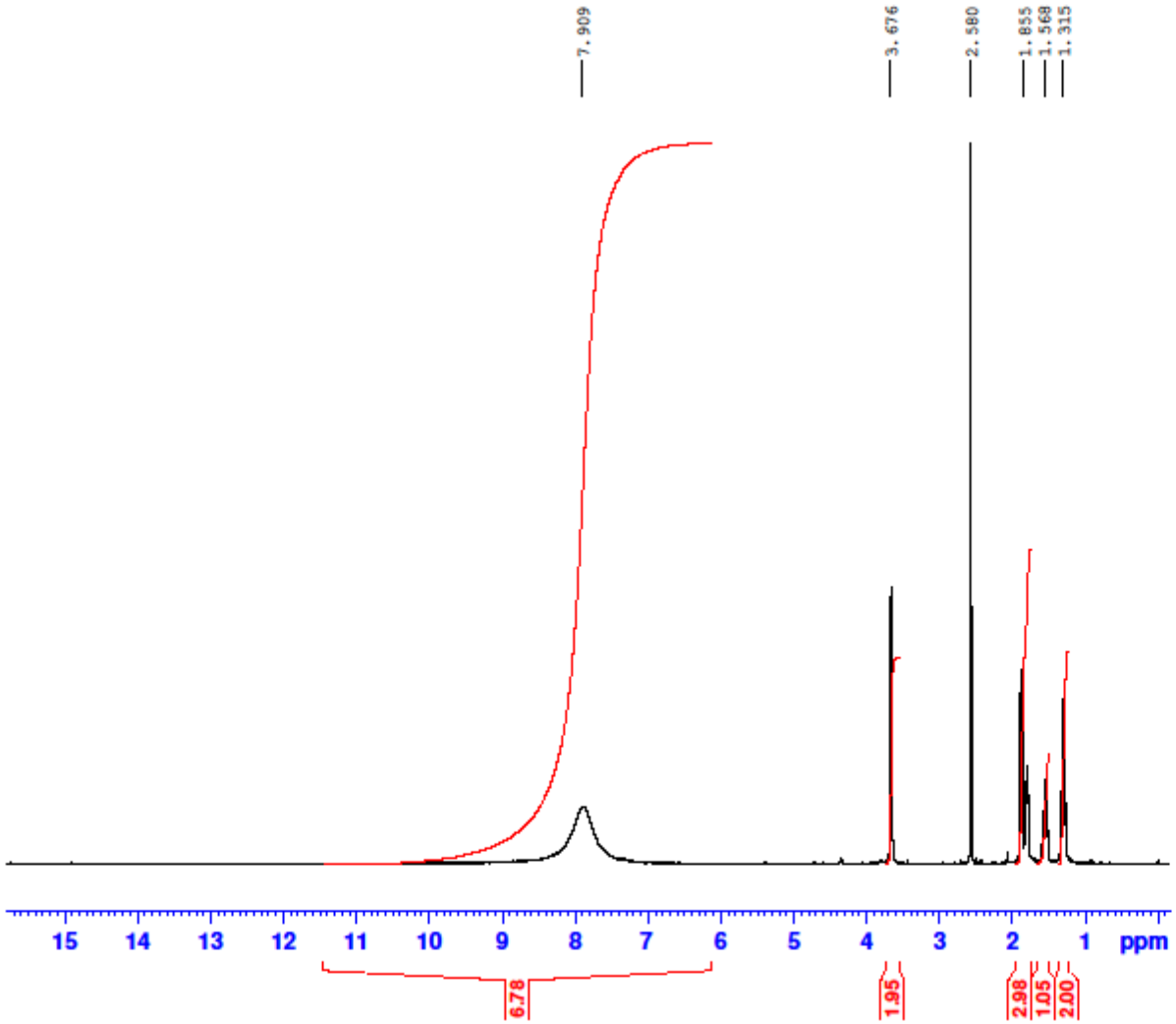
```
Current Data Parameters
NAME          JEP-489-058
EXPNO                  41
PROCNO                  1

F2 - Acquisition Parameters
Date_           20140820
Time              14.47
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT           DMSO
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                  724
DW               16.800 usec
DE                7.68 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

====== CHANNEL f1 ======
SFO1         125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1        82.38999939 W

====== CHANNEL f2 ======
SFO2         500.3020012 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.33600044 W
PLW12        0.75654000 W
PLW13        0.48418999 W

F2 - Processing parameters
SI               65536
SF           125.8005350 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



7a



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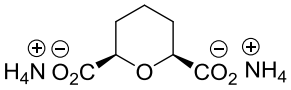
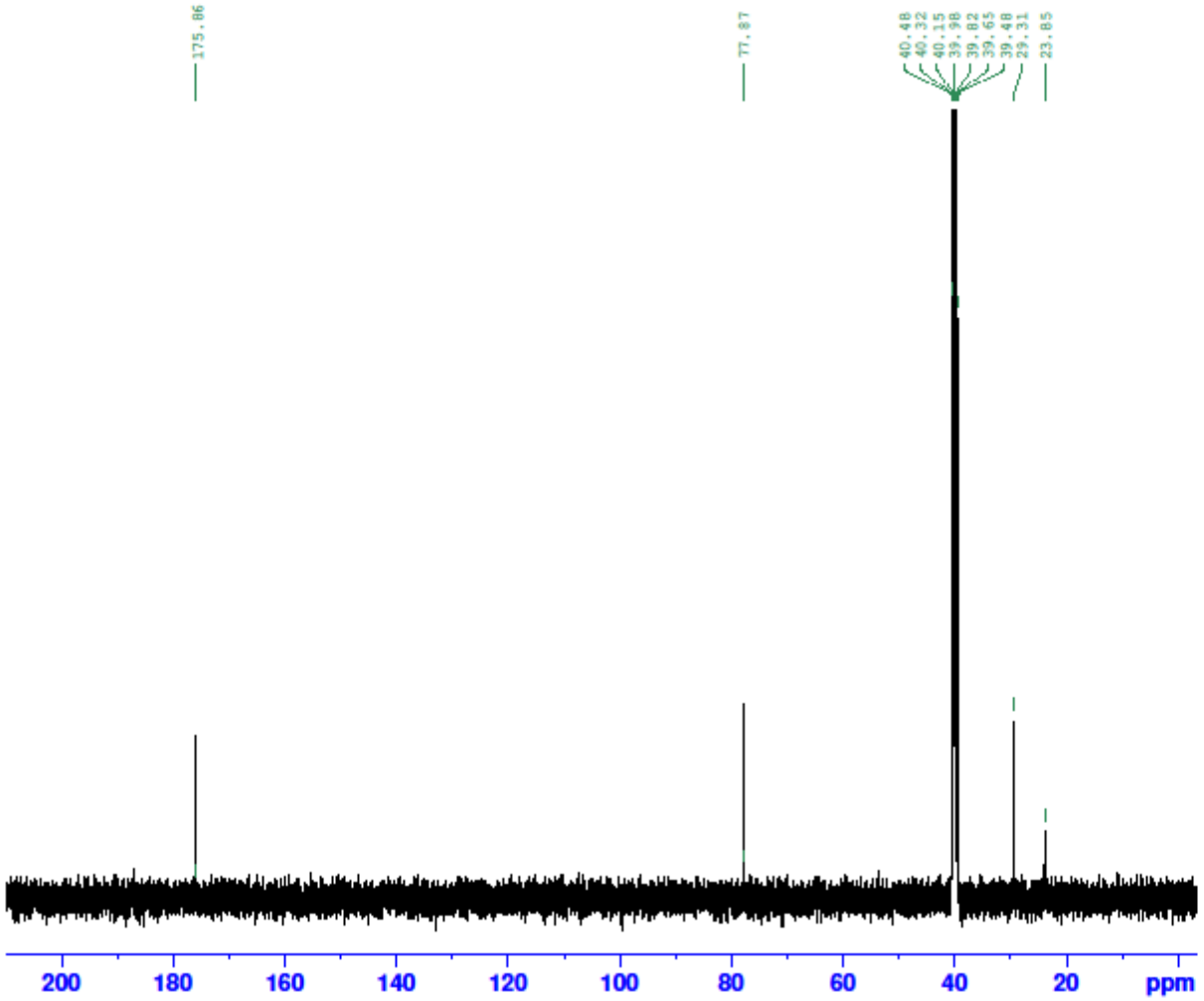
```
Current Data Parameters
NAME          JEP-489-152
EXPNO                  50
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150203
Time                15.37
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      0
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719425 sec
RG                    362
DW               48.400 usec
DE               11.99 usec
TE                292.7 K
D1           1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         500.3030896 MHz
NUC1                   1H
P1                  16.25 usec
PLW1         18.33600044 W

F2 - Processing parameters
SI                  65536
SF           500.2999679 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```



7a



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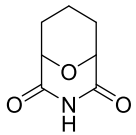
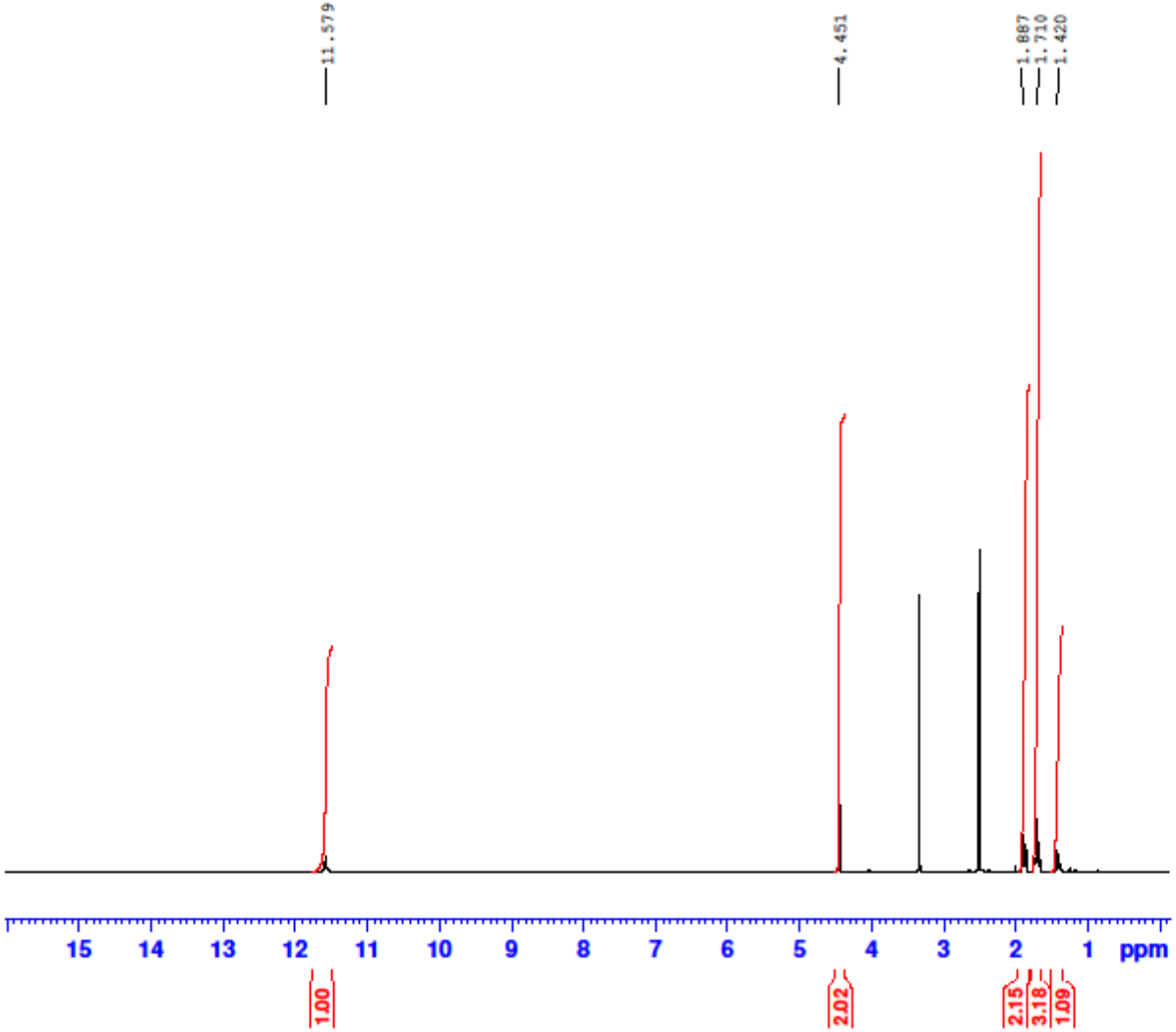
```
Current Data Parameters
NAME          JKP-489-152
EXPNO                  51
PROCNO                  1

F2 - Acquisition Parameters
Date_          20150203
Time              16.24
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT           DMSO
NS                  256
DS                    2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                  575
DW               16.800 usec
DE                7.68 usec
TE               295.7 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2               1H
CPDPRG[2        waltz16
PCPD2             80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                65536
SF           125.8005350 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



8a



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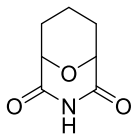
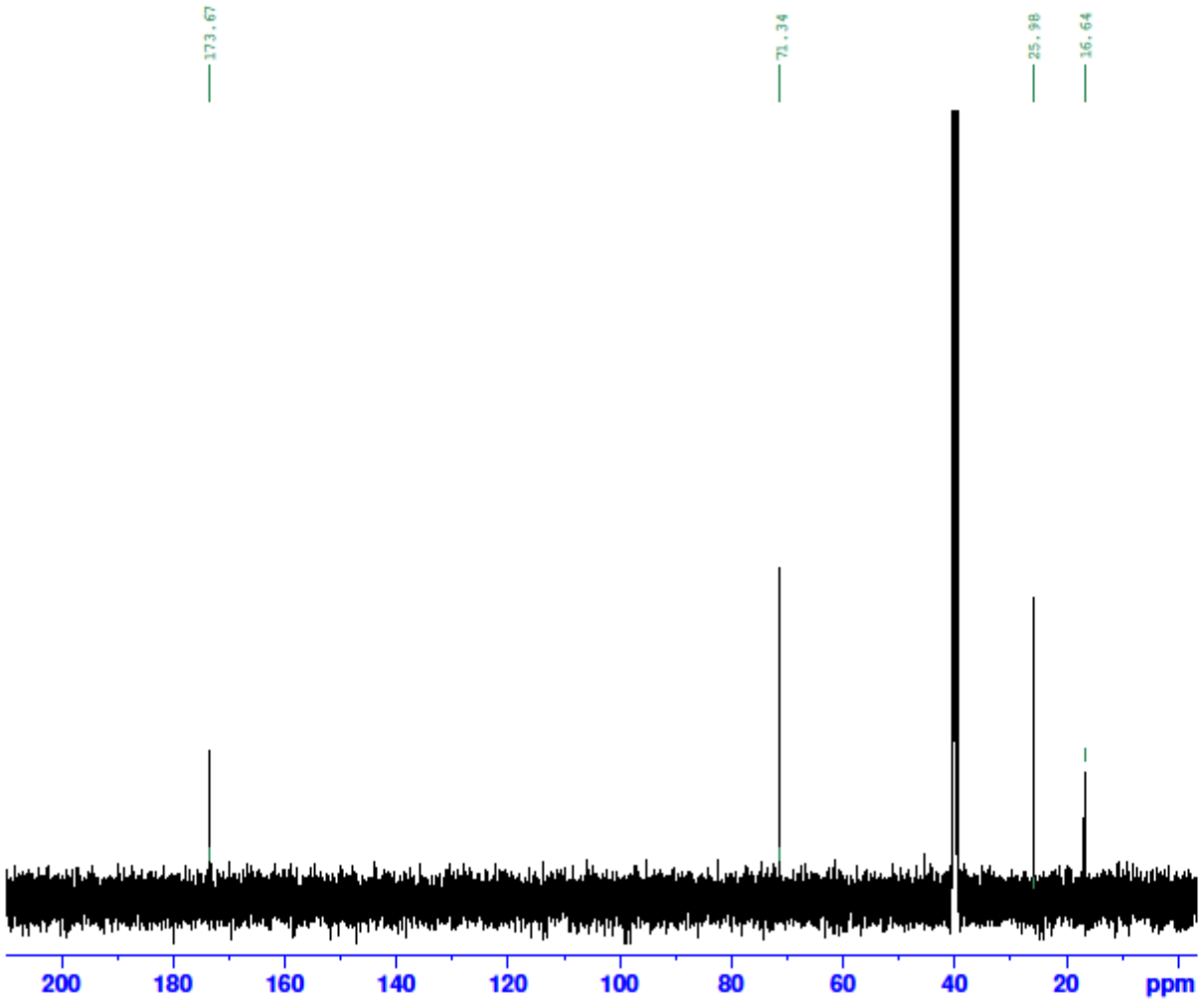
```
Current Data Parameters
NAME         JEP-489-090
EXPNO                 11
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141016
Time                8.51
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     0
SWH            10330.578 Hz
FIDRES         0.157632 Hz
AQ             3.1719425 sec
RG                   724
DW                48.400 usec
DE                11.99 usec
TE                295.3 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          500.3030896 MHz
NUC1                  1H
P1                 16.25 usec
PLW1          18.33600044 W

F2 - Processing parameters
SI                 65536
SF            500.3000000 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```



8a



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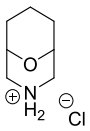
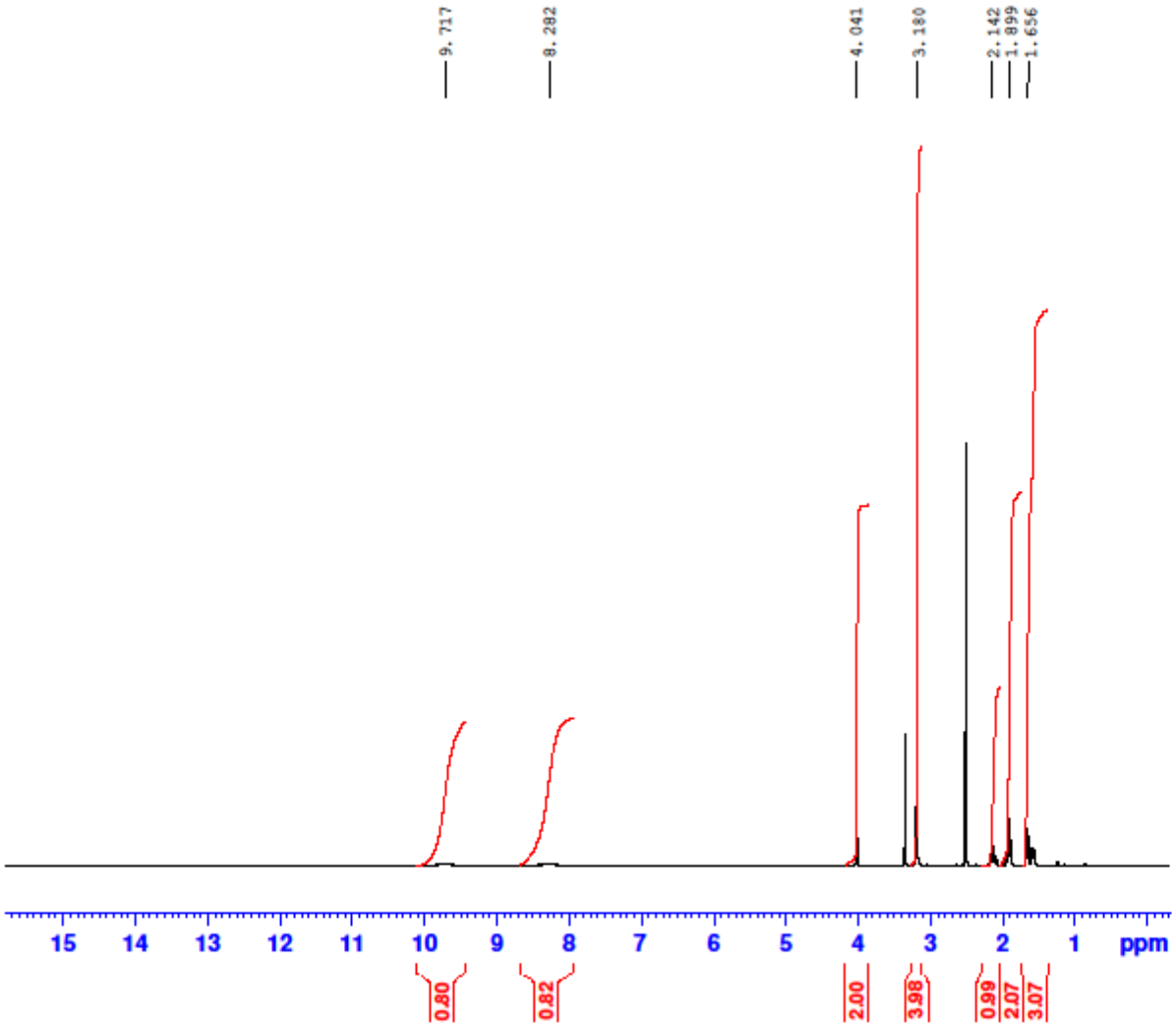
```
Current Data Parameters
NAME         JEP-489-090
EXPNO                 16
PROCNO                 1

F2 - Acquisition Parameters
Date_           20141016
Time              22.44
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT             DMSO
NS                    256
DS                      2
SWH             29761.904 Hz
FIDRES          0.454131 Hz
AQ              1.1010048 sec
RG                    456
DW                16.800 usec
DE                 7.68 usec
TE                298.5 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1                  13C
P1                   9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2               80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                 65536
SF           125.8005350 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



2a



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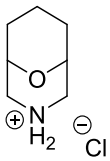
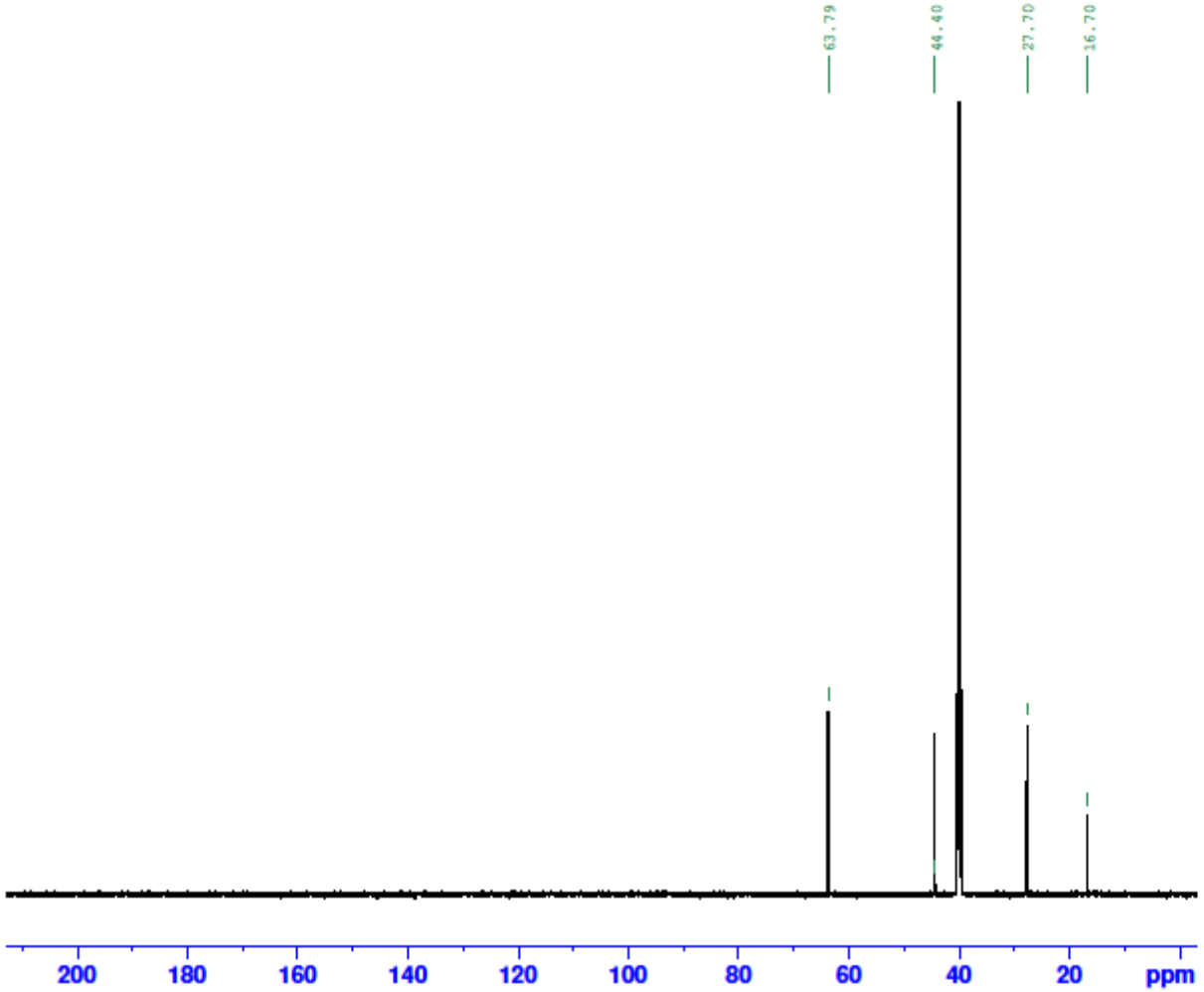
CANCER RESEARCH UK

```
Current Data Parameters
NAME          JEP-489-162
EXPNO                  20
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150213
Time                9.15
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     0
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719425 sec
RG                   575
DW              48.400 usec
DE              11.99 usec
TE              292.5 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1          500.3030896 MHz
NUC1                  1H
P1                16.25 usec
PLW1          18.33600044 W

F2 - Processing parameters
SI                 65536
SF            500.3000000 MHz
WDW                   EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```



2a



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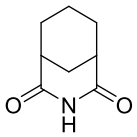
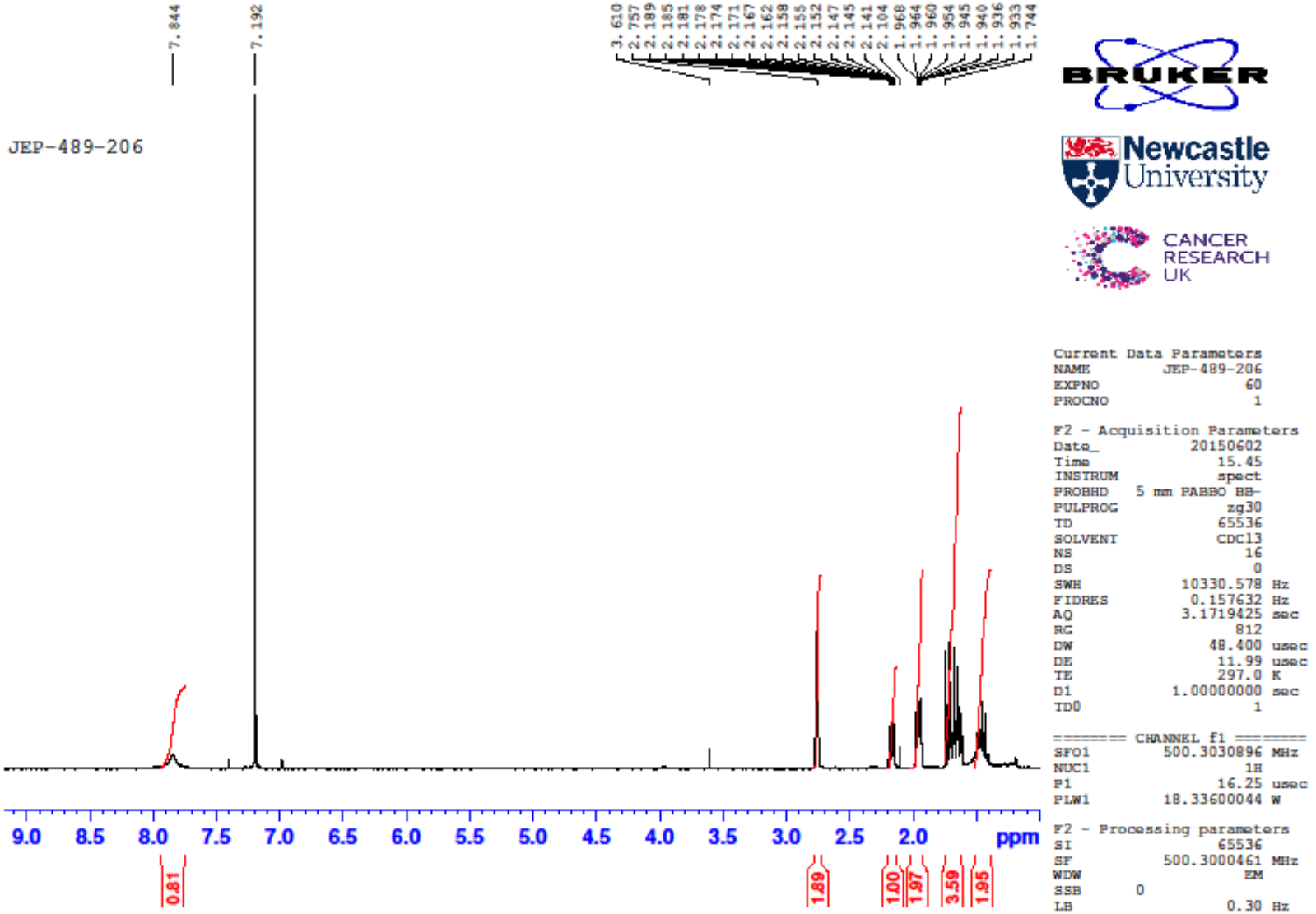
```
Current Data Parameters
NAME          JKP-489-162
EXPNO                  25
PROCNO                  1

F2 - Acquisition Parameters
Date_           20150214
Time                0.38
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zgpg
TD                 41662
SOLVENT             DMSO
NS                   2656
DS                      2
SWH           29761.904 Hz
FIDRES        0.714366 Hz
AQ            0.6999216 sec
RG                    456
DW               16.800 usec
DE                7.72 usec
TE                296.4 K
D1            5.00000000 sec
D11           0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1                  13C
P1                   9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2               80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                  65536
SF           125.8005350 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```



8b



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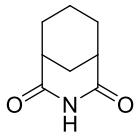
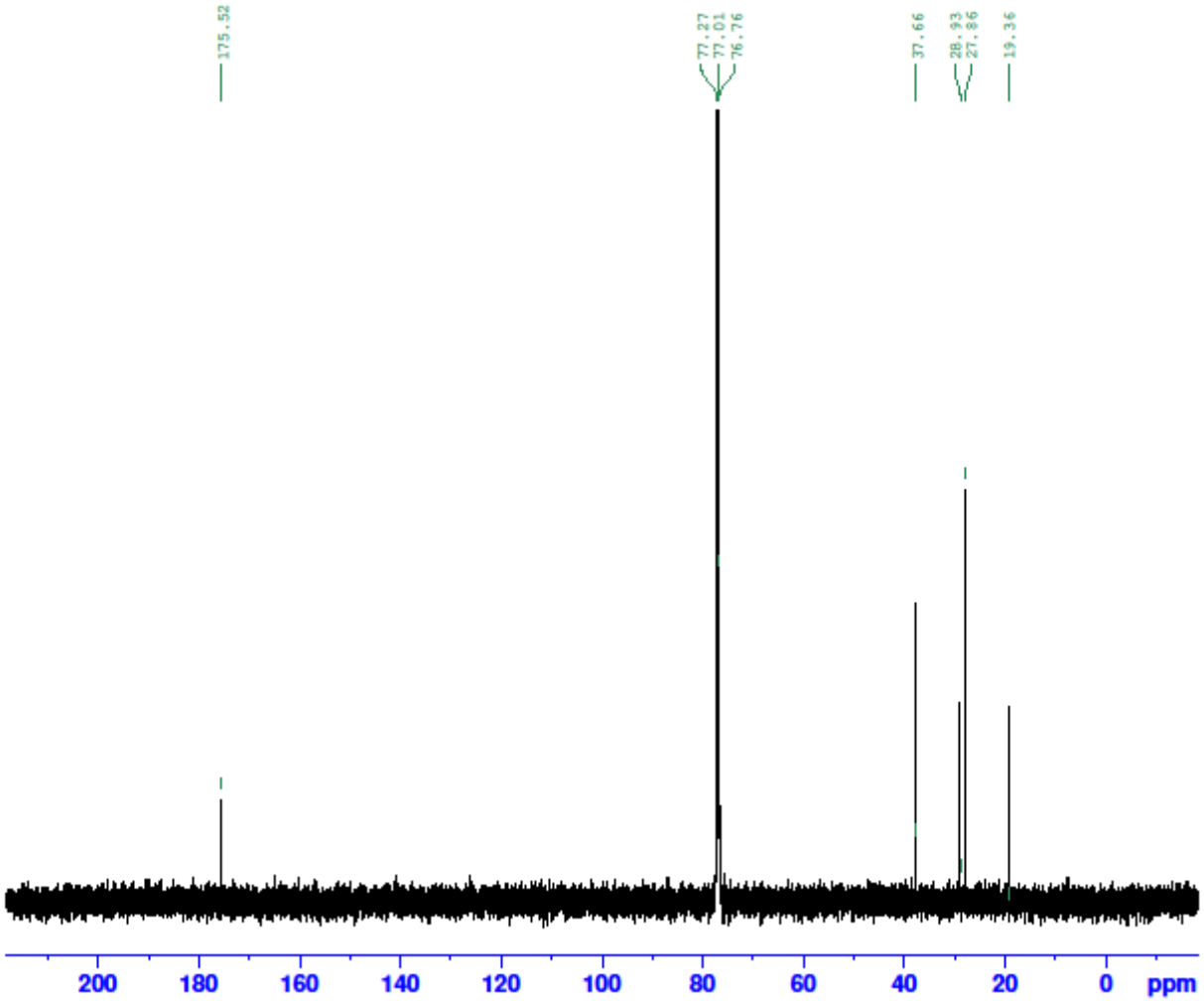
```
Current Data Parameters
NAME         JEP-489-206
EXPNO                 60
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150602
Time              15.45
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  16
DS                   0
SWH          10330.578 Hz
FIDRES        0.157632 Hz
AQ           3.1719425 sec
RG                 812
DW              48.400 usec
DE              11.99 usec
TE              297.0 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1        500.3030896 MHz
NUC1                1H
P1               16.25 usec
PLW1        18.33600044 W

F2 - Processing parameters
SI               65536
SF          500.3000461 MHz
WDW                 EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```



8b

JEP-489-206



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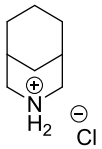
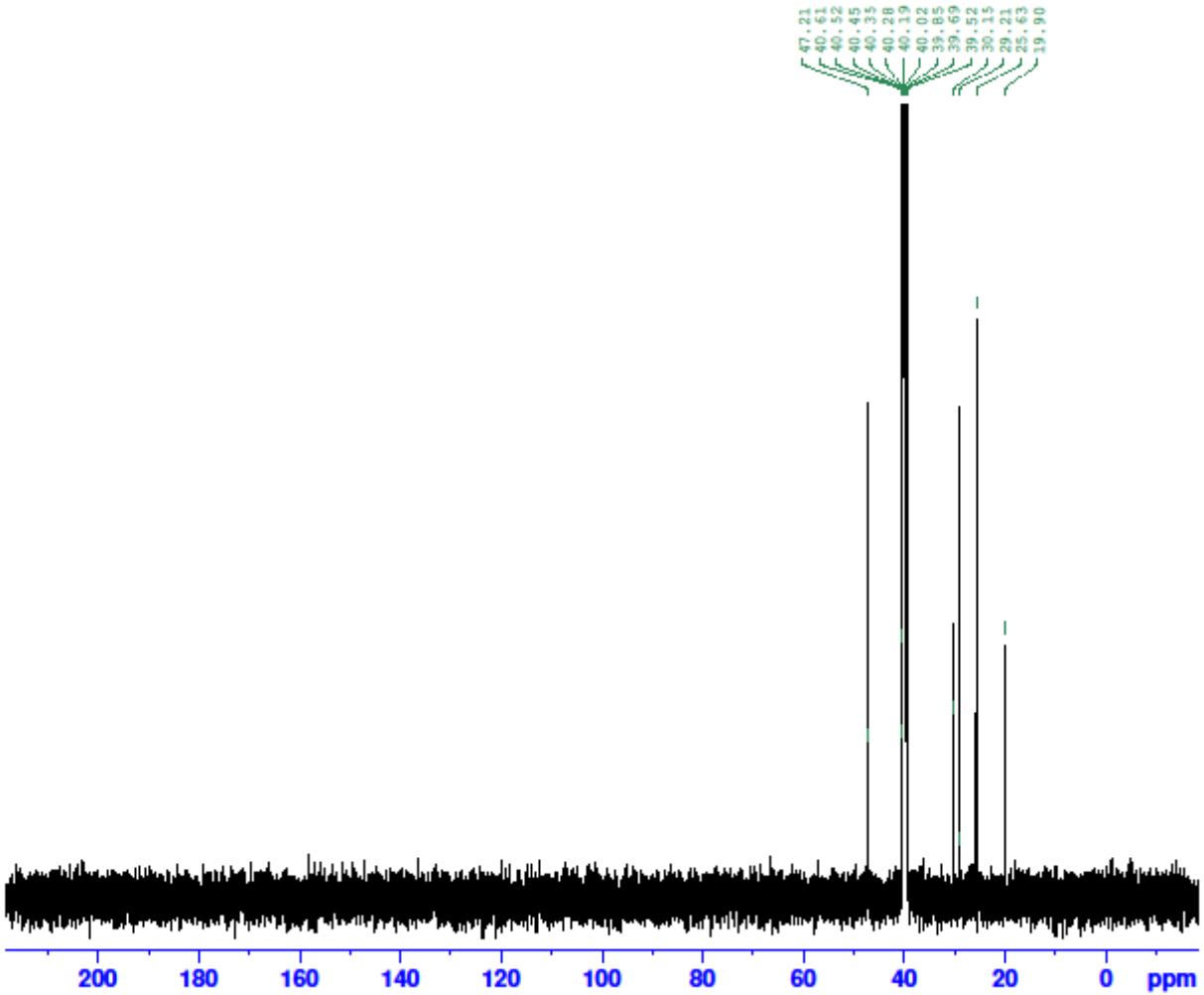
```
Current Data Parameters
NAME          JEP-489-206
EXPNO                  61
PROCNO                  1

F2 - Acquisition Parameters
Date_           20150603
Time               4.41
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 2560
DS                    2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                  456
DW               16.800 usec
DE                7.68 usec
TE               298.9 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2               1H
CPDPRG[2          waltz16
PCPD2             80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                65536
SF           125.8005350 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



2b

JEP-489-214



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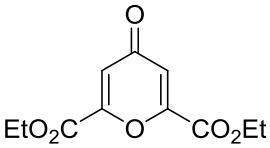
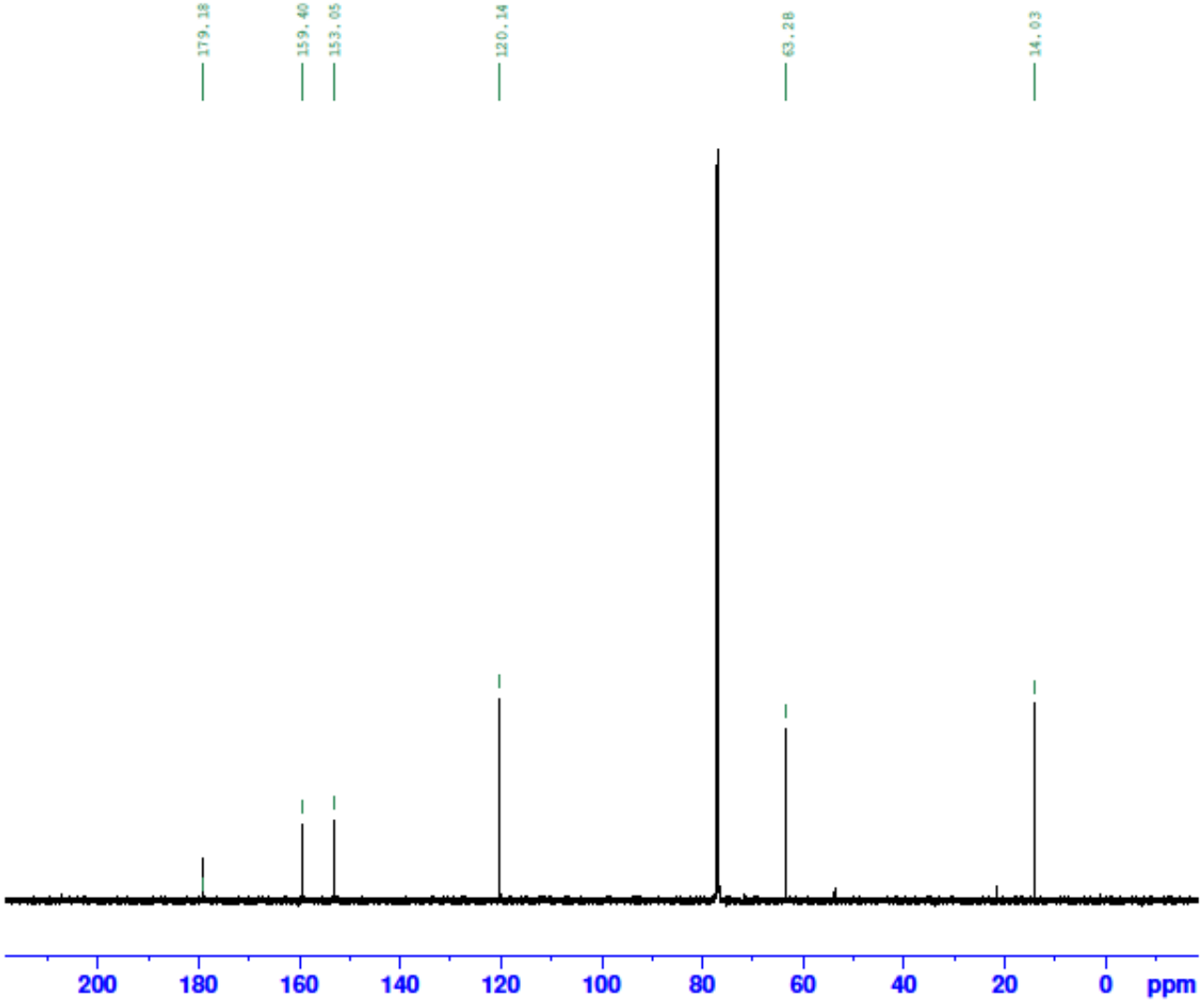
```
Current Data Parameters
NAME         JEP-489-214
EXPNO                 36
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150608
Time              20.56
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT             DMSO
NS                   2560
DS                      2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                    456
DW               16.800 usec
DE                7.68 usec
TE               298.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        125.8131151 MHz
NUC1                  13C
P1                   9.75 usec
PLW1        82.38999939 W

======== CHANNEL f2 ========
SFO2        500.3020012 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2               80.00 usec
PLW2        18.33600044 W
PLW12        0.75654000 W
PLW13        0.48418999 W

F2 - Processing parameters
SI                 65536
SF          125.8005350 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  1.40
```





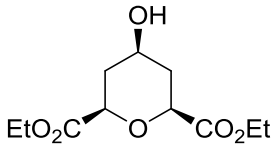
Current Data Parameters
NAME MA-502-76
EXPNO 32
PROCNO 1

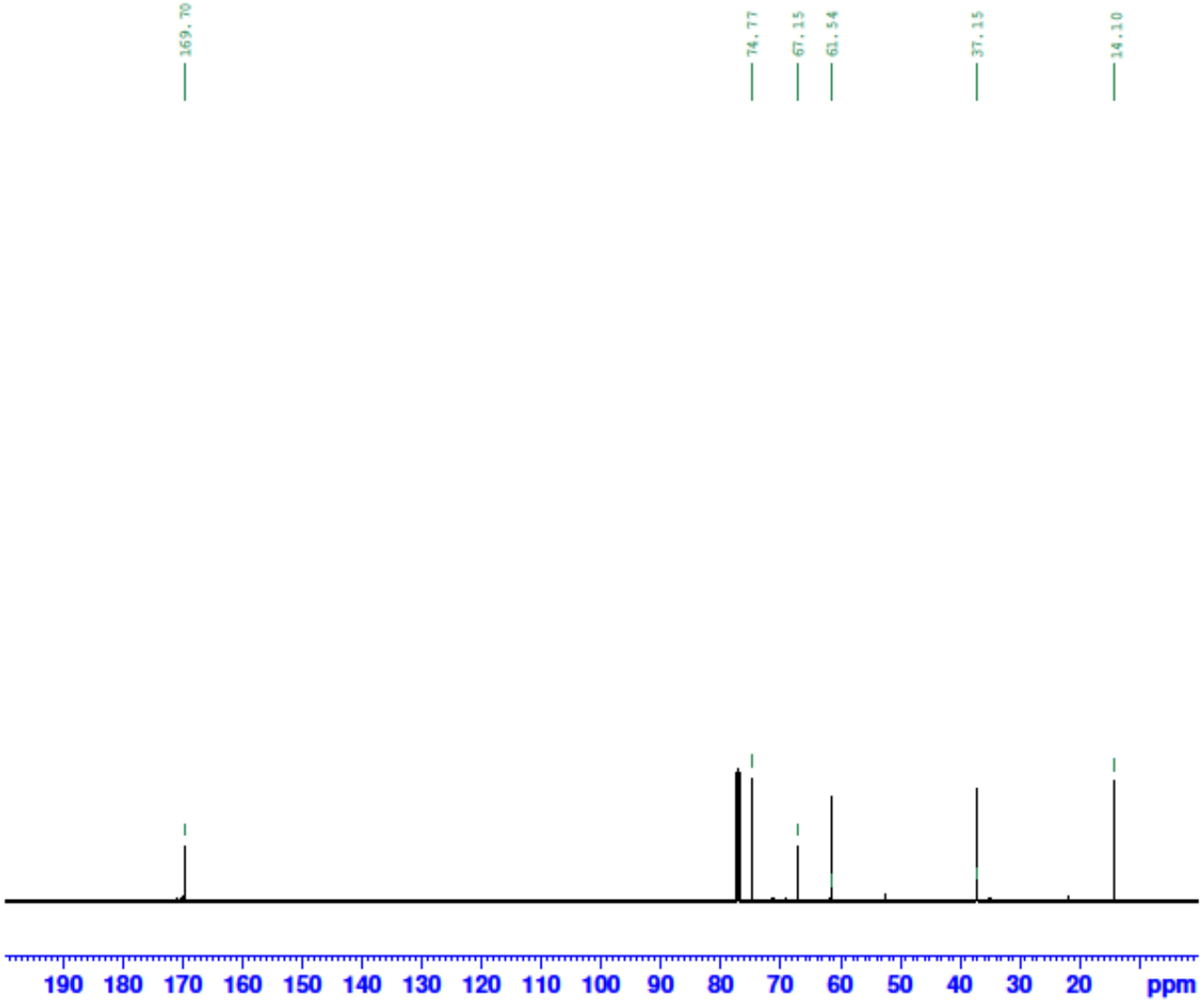
F2 - Acquisition Parameters
Date_ 20150701
Time 4.49
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 2
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 456
DW 16.800 usec
DE 7.68 usec
TE 299.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1

====== CHANNEL f1 ======
SFO1 125.8131151 MHz
NUC1 13C
P1 9.75 usec
PLW1 82.38999939 W

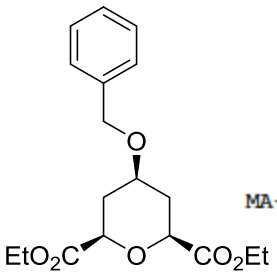
====== CHANNEL f2 ======
SFO2 500.3020012 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 18.33600044 W
PLW12 0.75654000 W
PLW13 0.48418999 W

F2 - Processing parameters
SI 65536
SF 125.8005350 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

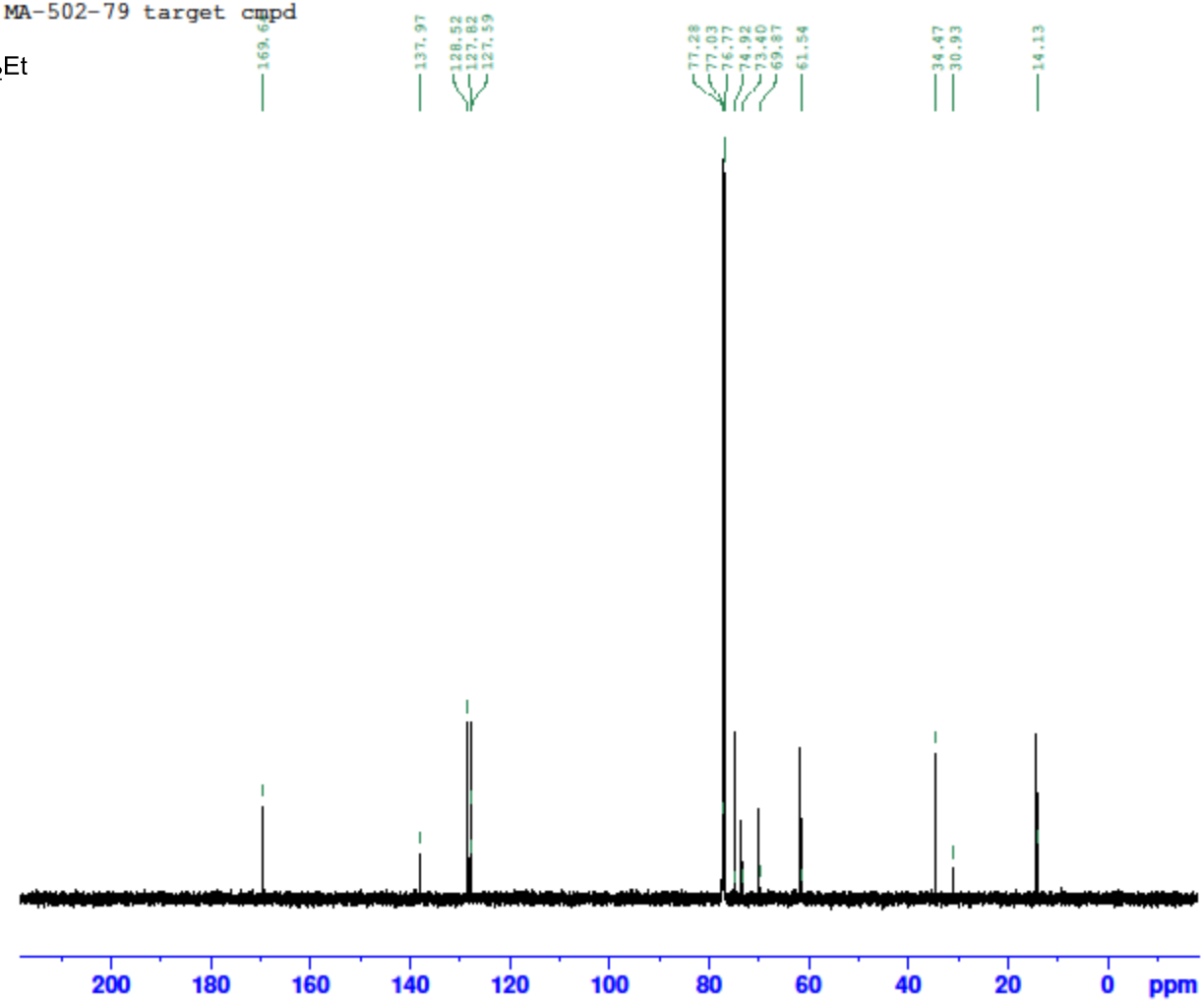





```
Current Data Parameters
NAME      ma-502-81(20-30)
EXPNO                  13
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150709
Time                1.37
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT            CDCl3
NS                  1024
DS                     2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                   456
DW               16.800 usec
DE                7.68 usec
TE               298.0 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1                 13C
P1                  9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2              80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                 65536
SF           125.8005350 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```



MA-502-79 target cmpd



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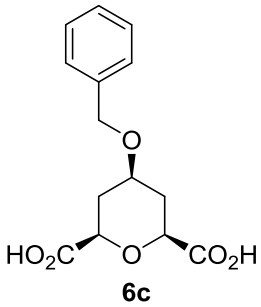
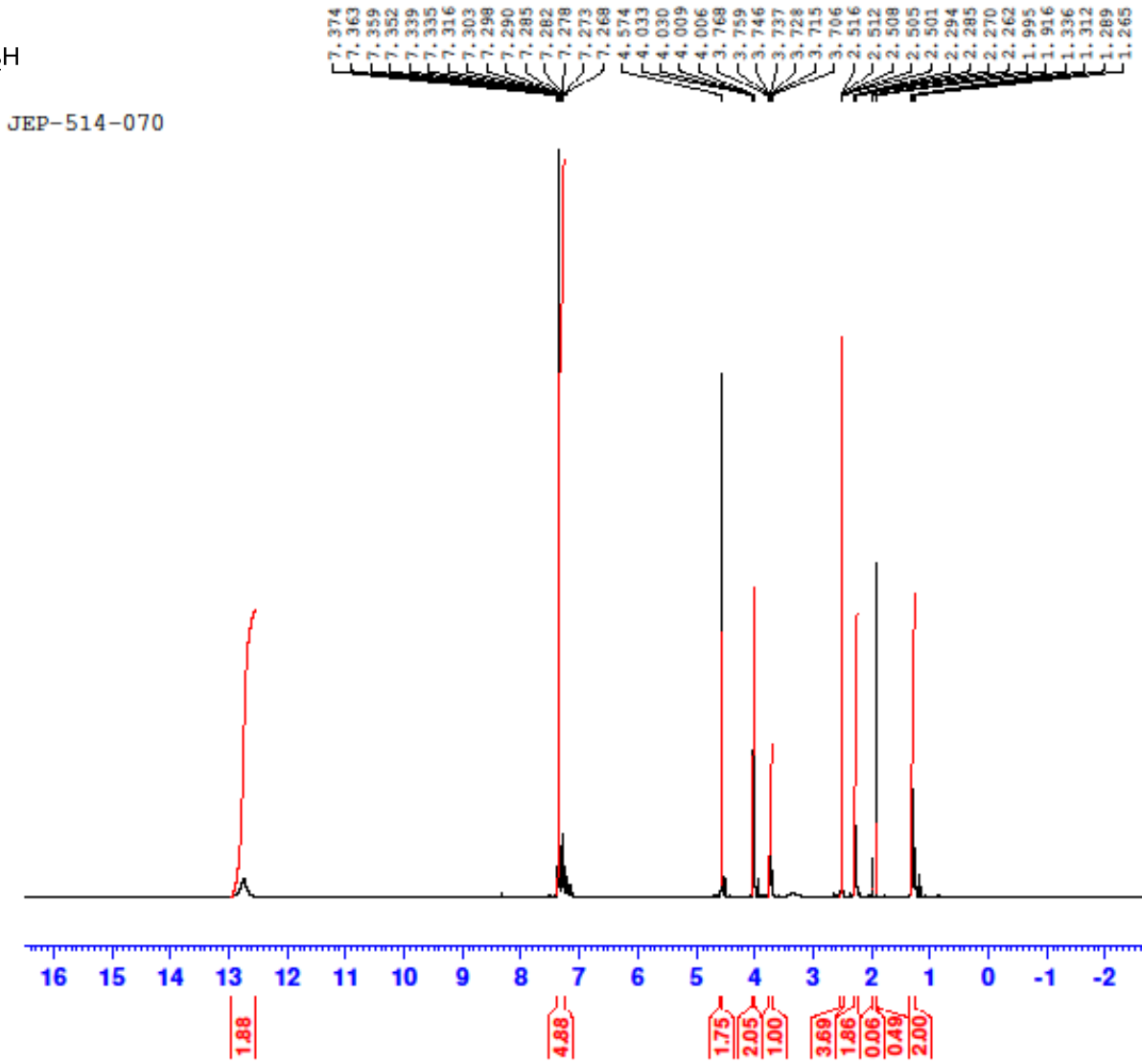
```
Current Data Parameters
NAME      MA-502-79 target cmpd
EXPNO                13
PROCNO                1

F2 - Acquisition Parameters
Date_          20150706
Time              20.57
INSTRUM           spect
PROBHD   5 mm PABBO BB-
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 256
DS                   2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                 575
DW               16.800 usec
DE                7.68 usec
TE               298.9 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1              13c
P1                9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2              1H
CPDPRG[2        waltz16
PCPD2            80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI               65536
SF           125.8005350 MHz
WDW                 EM
SSB          0
LB                1.00 Hz
GB           0
PC                1.40
```



6c

JEP-514-070



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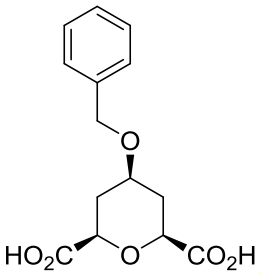
```
Current Data Parameters
NAME          JEP-514-070
EXPNO                  20
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150814
Time                15.15
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                     16
DS                      0
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719425 sec
RG                    322
DW               48.400 usec
DE               11.99 usec
TE               296.9 K
D1            1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         500.3030896 MHz
NUC1                   1H
P1                16.25 usec
PLW1         18.33600044 W

F2 - Processing parameters
SI                  65536
SF           500.3000000 MHz
WDW                    EM
SSB          0
LB                  0.30 Hz
GB           0
PC                  1.00
```



6c

JEP-514-070

172.48
171.65
141.00
139.69
139.19
136.83
136.79
130.49
129.32
129.15
129.13
129.06
128.88
128.81
128.75
128.72
128.50
128.22
128.17
127.92
127.89
127.87
127.84
127.08
126.88
126.66
126.41
73.98
73.65
73.43
73.27
69.28
69.05
67.59
63.35
41.27
40.58
40.49
40.41
40.32
40.25
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34.92
34.80
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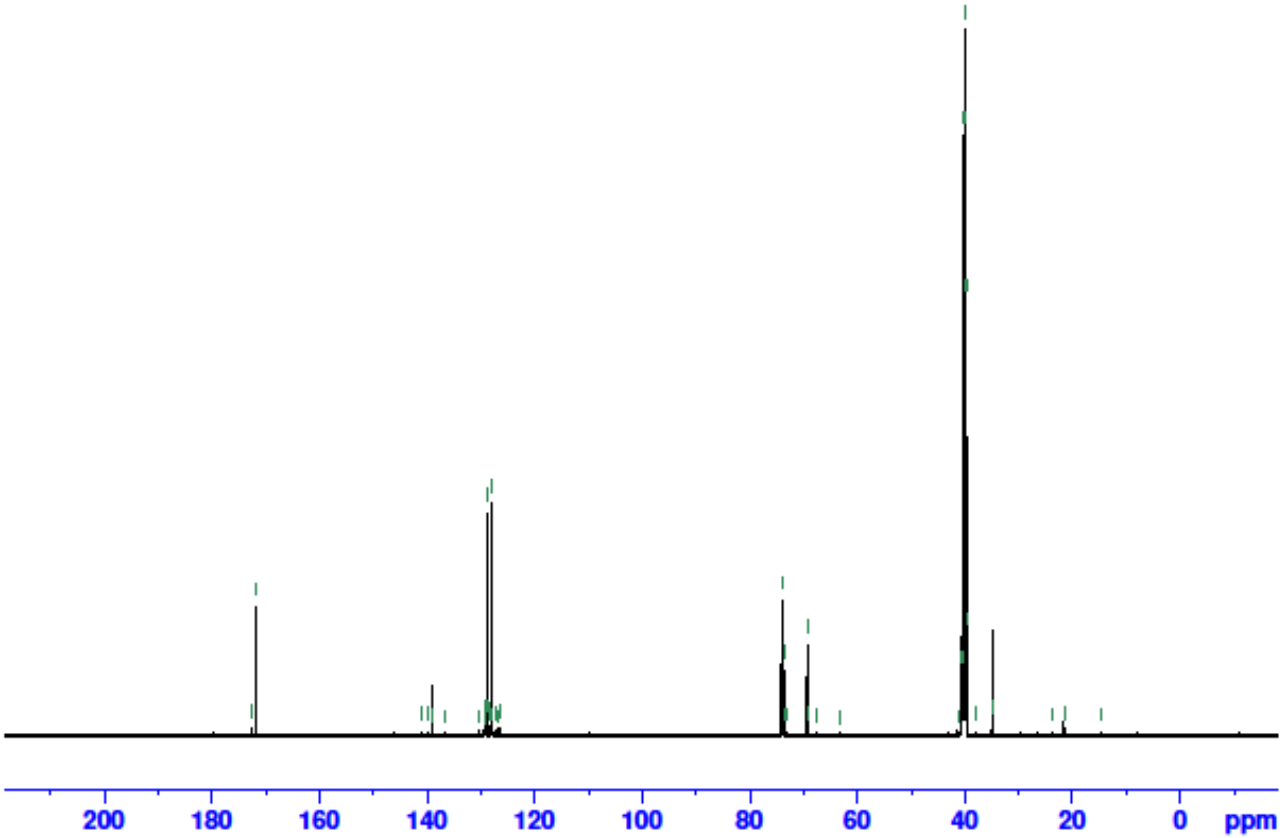
14.56



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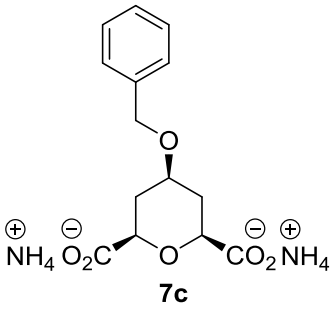
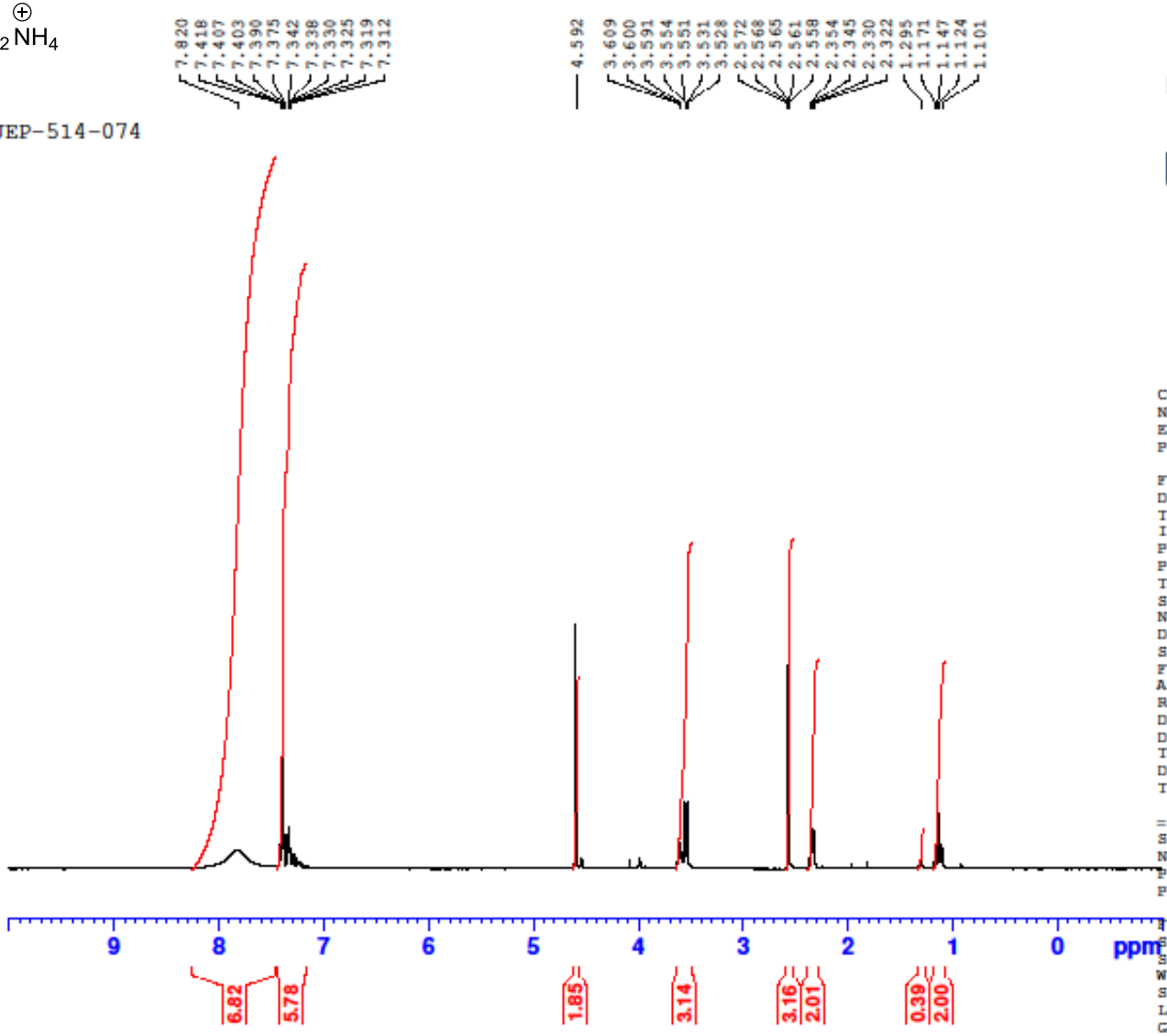
```
Current Data Parameters
NAME          JEP-514-070
EXPNO                  21
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150815
Time               11.53
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg
TD                 41662
SOLVENT             DMSO
NS                  2656
DS                     2
SWH           29761.904 Hz
FIDRES        0.714366 Hz
AQ            0.699216 sec
RG                   456
DW              16.800 usec
DE               7.72 usec
TE               297.9 K
D1           5.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1        125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1        82.38999939 W

======== CHANNEL f2 ========
SFO2        500.3020012 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2        18.33600044 W
PLW12        0.75654000 W
PLW13        0.48418999 W

F2 - Processing parameters
SI                 65536
SF          125.8005350 MHz
WDW                EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



JEP-514-074



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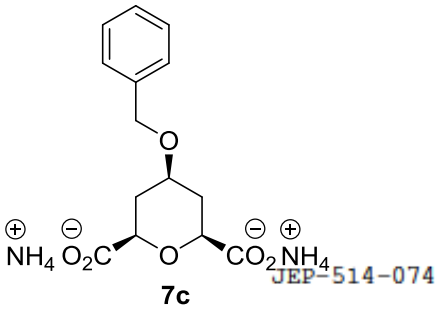
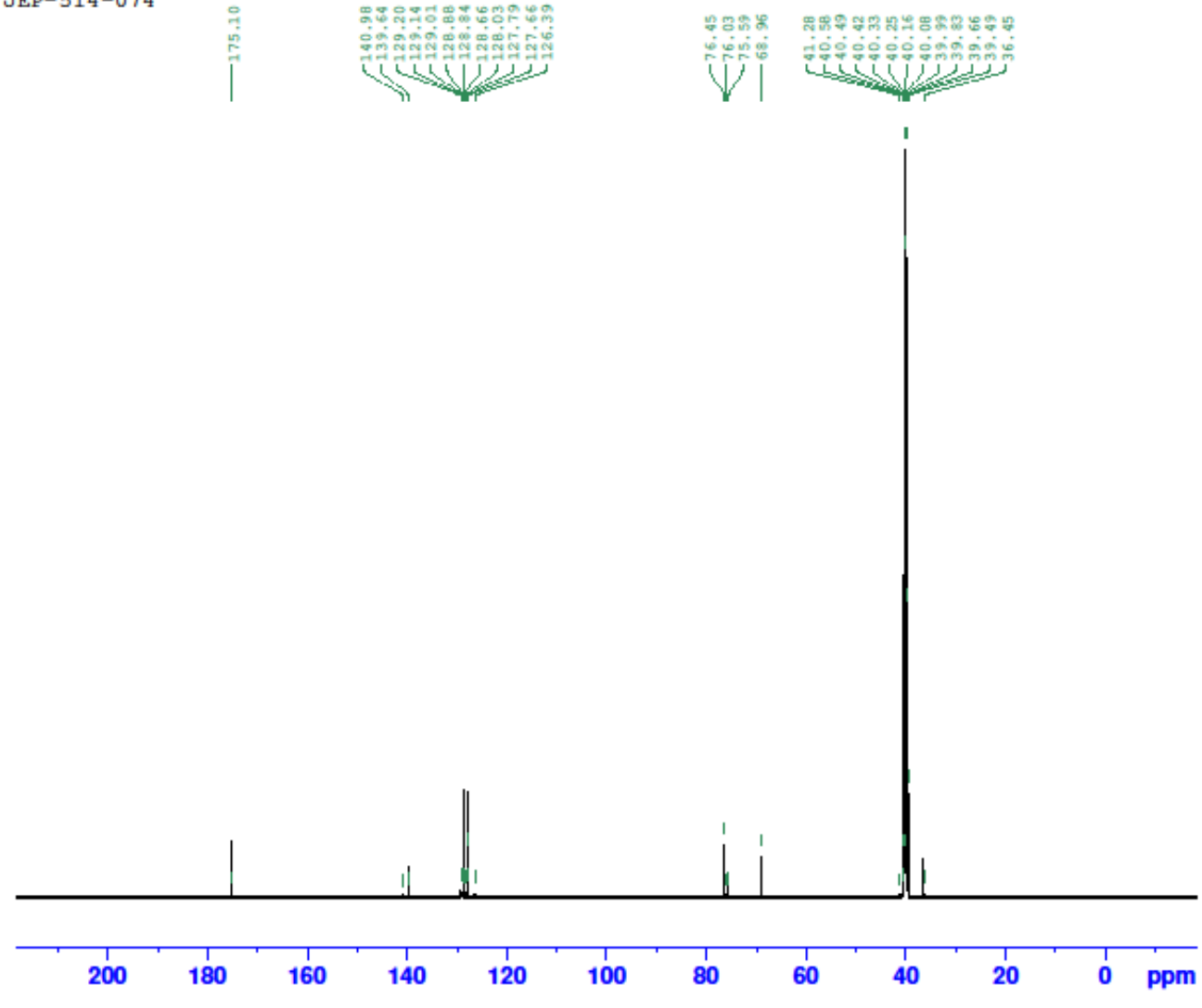
```
Current Data Parameters
NAME          JEP-514-074
EXPNO                  10
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150818
Time                8.41
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT              DMSO
NS                      16
DS                       0
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719425 sec
RG                     256
DW               48.400 usec
DE               11.99 usec
TE                297.0 K
D1           1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         500.3030896 MHz
NUC1                   1H
P1                16.25 usec
PLW1         18.33600044 W

F2 - Processing parameters
SI                  65536
SF           500.2999717 MHz
WDW                    EM
SSB          0
LB                0.30 Hz
GB           0
PC                1.00
```





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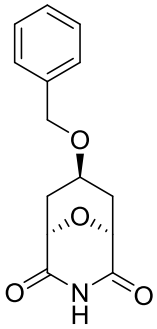
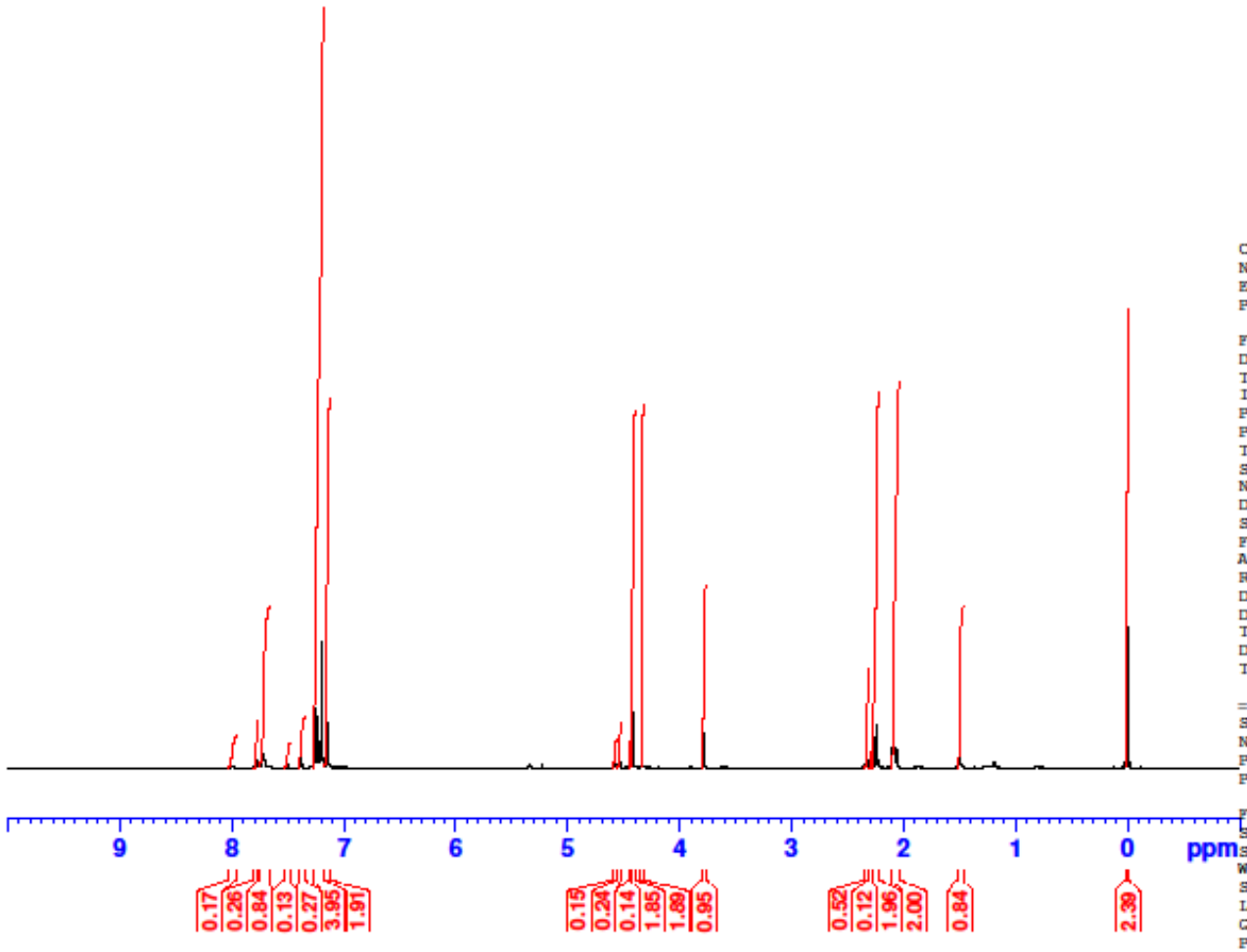
```
Current Data Parameters
NAME          JEP-514-074
EXPNO                  14
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150818
Time                21.45
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                  2560
DS                     2
SWH           29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                   575
DW               16.800 usec
DE                7.68 usec
TE               297.5 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1         82.38999939 W

======== CHANNEL f2 ========
SFO2         500.3020012 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2             80.00 usec
PLW2         18.33600044 W
PLW12         0.75654000 W
PLW13         0.48418999 W

F2 - Processing parameters
SI                 65536
SF           125.8005350 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```



8c

JEP-514-078



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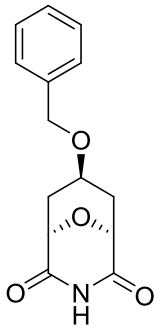
CANCER RESEARCH UK

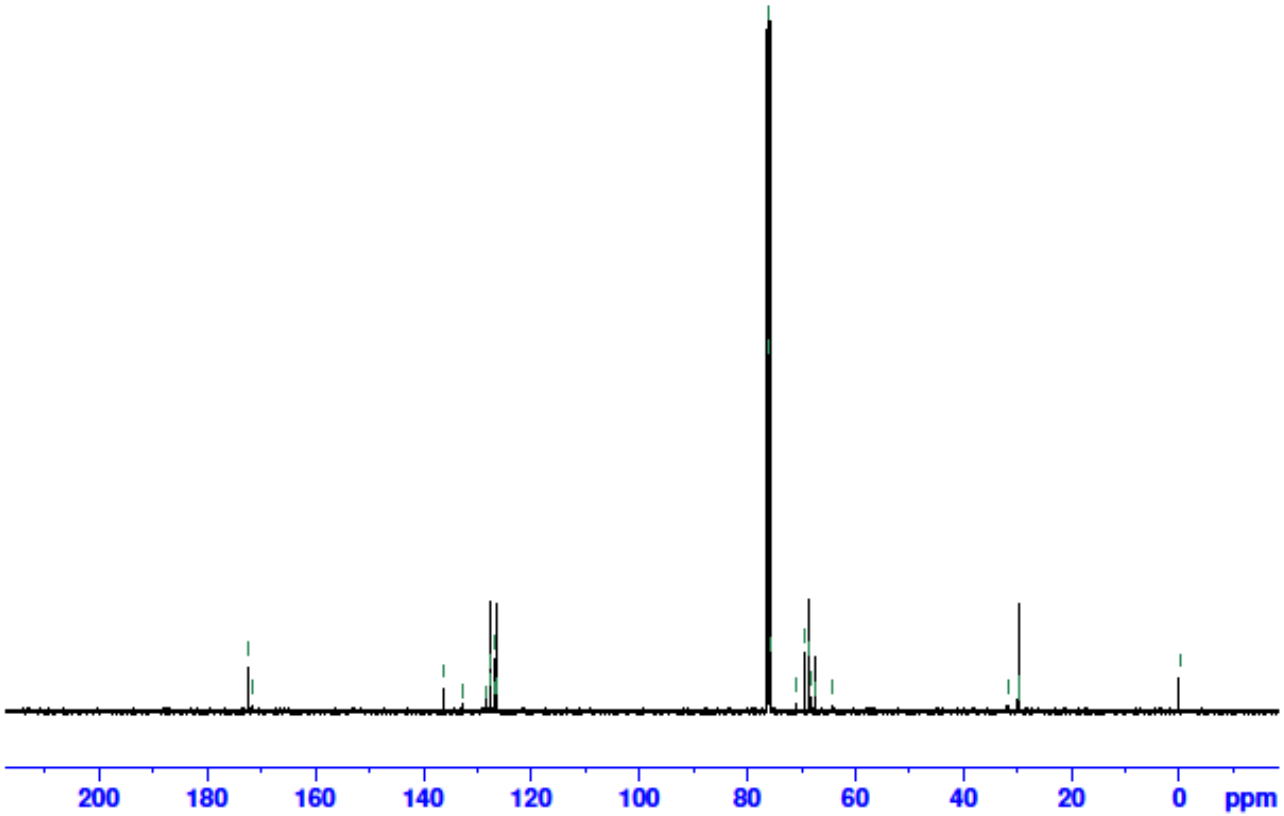
```
Current Data Parameters
NAME          JEP-514-078
EXPNO                  60
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150821
Time                16.14
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      0
SWH           10330.578 Hz
FIDRES         0.157632 Hz
AQ            3.1719425 sec
RG                    512
DW               48.400 usec
DE               11.99 usec
TE                297.3 K
D1           1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         500.3030896 MHz
NUC1                   1H
P1                 16.25 usec
PLW1         18.33600044 W

F2 - Processing parameters
SI                  65536
SF           500.3000467 MHz
WDW                    EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```



8c

JEP-514-078

172.32
171.57
136.28
132.52
128.47
127.69
127.55
127.42
126.95
126.71
126.56
126.31
76.25
75.99
75.74
70.89
69.47
68.54
68.24
67.52
64.27
31.80
29.87
29.76
0.00



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```
Current Data Parameters
NAME          JEP-514-078
EXPNO                  66
PROCNO                  1

F2 - Acquisition Parameters
Date_           20150822
Time                5.20
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 2560
DS                    2
SWH          29761.904 Hz
FIDRES        0.454131 Hz
AQ            1.1010048 sec
RG                  724
DW               16.800 usec
DE                7.68 usec
TE              298.3 K
D1            2.00000000 sec
D11           0.03000000 sec
TD0                   1

====== CHANNEL f1 ======
SFO1        125.8131151 MHz
NUC1               13C
P1                9.75 usec
PLW1        82.38999939 W

====== CHANNEL f2 ======
SFO2        500.3020012 MHz
NUC2               1H
CPDPRG[2        waltz16
PCPD2             80.00 usec
PLW2        18.33600044 W
PLW12        0.75654000 W
PLW13        0.48418999 W

F2 - Processing parameters
SI                65536
SF          125.8006643 MHz
WDW                  EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```